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DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

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CENTER FOR DEVICES AND RADIOLOGICAL HEALTH

MEDICAL DEVICES ADVISORY COMMITTEE

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GASTROENTEROLOGY AND UROLOGY DEVICES PANEL

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February 25, 2016
8:00 a.m.

Hilton Washington DC North
620 Perry Parkway
Gaithersburg, Maryland

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ASHLEY L. FAULX, M.D.	Voting Member
SUSAN J. KALOTA, M.D.	Voting Member
CHERYL IGLESIA, M.D.	Temporary Voting Member
ABDELMONEM A. AFIFI, Ph.D.	Temporary Voting Member
JONATHAN EFRON, M.D.	Temporary Voting Member
TERRY HICKS, M.D.	Temporary Voting Member
JASON CONNOR, Ph.D.	Temporary Voting Member
BARBARA BERNEY	Patient Representative
MILDRED FENNAL, M.S.N., Ph.D.	Consumer Representative
CRAIG F. DONATUCCI, M.D.	Industry Representative
LCDR PATRICIO G. GARCIA, M.P.H.	Designated Federal Officer

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M E E T I N G

(8:01 a.m.)

DR. TALAMINI: Good morning, everyone. I've got 8:01. I would like to call this meeting of the Gastroenterology and Urology Devices Panel of the Medical Devices Advisory Committee to order.

I am Dr. Mark Talamini, the Chair of the Panel. I'm the Chairman of the Department of Surgery at SUNY Stony Brook on Long Island, and I practice as a gastrointestinal surgeon.

I note for the record that the voting members present constitute a quorum as required by 21 C.F.R. Part 14. I would also like to add that the Panel members participating in today's meeting have received training in FDA device law and regulations.

For today's agenda, the Panel will discuss, make recommendations, and vote on information regarding the premarket approval application for TOPAS Treatment for Fecal Incontinence device for the treatment of fecal incontinence, by ASTORA Women's Health, LLC.

Before we begin, I would like to ask our distinguished Panel members and FDA staff seated at the table to introduce themselves. Please state your name, your area of expertise, your position, and affiliation.

And, Dr. Fisher, could we start with you, please?

DR. FISHER: Good morning. My name is Ben Fisher. I'm the Director of the Division of Reproductive, Gastro-Renal, and Urological Devices at FDA.

DR. KALOTA: Hello, I'm Susan Kalota. I am a private practice urologist in Tucson, Arizona, with a specialty in urogynecology.

DR. EFRON: Hello, my name is Jonathan Efron. I am the Vice Chair of the Department of Surgery at Johns Hopkins University and the Chief of Colorectal Surgery there, and I am a colorectal surgeon.

DR. HICKS: I'm Terry Hicks. I am the Vice Chair of the Department of Colorectal Surgery at the Ochsner clinic in New Orleans.

LCDR GARCIA: My name's Patricio Garcia. I'm the Designated Federal Officer for this meeting.

DR. TALAMINI: Again, my name is Mark Talamini.

DR. IGLESIA: Hi, I'm Cheryl Iglesia. I am a urogynecologist. I am a Professor of OB/GYN and Urology at Georgetown University School of Medicine, and I direct the section for female pelvic medicine and reconstructive surgery for MedStar Health.

DR. CONNOR: Jason Connor, a statistician with Berry Consultants and an associate professor at the University of Central Florida College of Medicine, and I guess my expertise is clinical trial design and Bayesian adaptive trials.

DR. DONATUCCI: Craig Donatucci. I am a urologist. I am currently senior medical fellow at Eli Lilly, and I serve as the Industry Representative.

DR. FENNAL: Good morning. My name is Dr. Mildred Fennal. I am a retired nursing professor from Florida A&M University. I am acting now as the Director of the International Nursing Education Consortium, and my background is critical care and advanced medical surgical nursing.

MS. BERNEY: My name is Barbara Berney, and I am the Patient Representative, and I don't have credentials, but I have a lot of experience.

(Laughter.)

DR. TALAMINI: Fair enough.

Members of the audience, if you have not already done so, please sign the attendance sheets that are on the tables at the doors outside.

Lieutenant Commander Patricio Garcia is the Designated Federal Officer for the Gastroenterology and Urology Devices Panel. He will now make some introductory remarks.

Lieutenant Commander Garcia.

LCDR GARCIA: Thank you, Dr. Talamini.

The Food and Drug Administration is convening today's meeting of the Gastroenterology and Urology Devices Panel of the Medical Devices Advisory Committee under the authority of the Federal Advisory Committee Act (FACA) of 1972. With the exception of the Industry Representative, all members and consultants of the Panel are special Government employees or regular Federal employees from other agencies and are subject to Federal conflict of interest laws and regulations.

The following information on the status of this Panel's compliance with Federal ethics and conflict of interest laws covered by, but not limited to, those found at 18 United States Code Subparagraph 208 are being provided to participants in today's meeting and to the public.

FDA has determined that members and consultants of this Panel are in compliance with the Federal ethics and conflict of interest laws. Under Title 18 United States Code Subparagraph 208, Congress has authorized FDA to grant waivers to special Government

employees or regular Federal employees who have financial conflicts when it is determined that the Agency's need for a particular individual's services outweighs his or her potential financial conflict of interest.

Related to the discussion of today's meeting, members and consultants of this Panel who are special Government employees or regular Federal employees have been screened for potential financial conflicts of interest of their own as well as those imputed to them, including those of their spouses or minor children and, for the purpose of Title 18 United States Code Subparagraph 208, their employers. These interests may include investments; consulting; expert witness testimony; contracts/grants/CRADAs; teaching/speaking/writing; patents and royalties; and primary employment.

For today's agenda, the Panel will discuss and make recommendations and vote on information regarding the premarket approval application for TOPAS Treatment for Fecal Incontinence, by ASTORA Women's Health, LLC. The TOPAS Treatment for Fecal Incontinence is intended to treat women with fecal incontinence (also referred to as accidental bowel leakage) who have failed more conservative therapies.

Based on the agenda for today's meeting and all financial interests reported by the Panel members and consultants, no conflict of interest waivers have been issued in accordance with Title 18 United States Code Subparagraph 208.

Dr. Craig Donatucci is serving as the Industry Representative, acting on behalf of all related industry, and is employed by Eli Lilly Corporation.

We would like to remind members and consultants that if the discussion involves any other product or firm not already on the agenda for which an FDA participant has a

personal or imputed financial interest, the participants need to exclude themselves from such involvement and their exclusion will be noted for the record. FDA encourages all other participants to advise the Panel of any financial relationships that they may have with any firm at issue.

A copy of this statement will be available for review at the registration table during this meeting and will be included as a part of the official transcript.

I will now read the Appointment to Temporary Voting Status statement.

Pursuant to the authority granted under the Medical Devices Advisory Committee Charter of the Center for Devices and Radiological Health, dated October 27th, 1990, and as amended August 18th, 2006, I appoint the following individuals as voting members of the Gastroenterology and Urology Devices Panel for the duration of the meeting on February 25th, 2016.

Dr. Abdelmonem Afifi, Dr. Jonathan Efron, Dr. Jason Connor, Dr. Cheryl Iglesia, Dr. Terry Hicks.

For the record, these individuals are special Government employees who have undergone customary conflict of interest review and have reviewed the materials to be considered at this meeting.

This has been signed by Dr. Jeffrey Shuren, Director of the Center for Devices and Radiological Health, on February 10th, 2016.

A copy of this statement will be available for review at the registration table during this meeting and will be included as part of the official transcript.

Before I turn this back over to Dr. Talamini, I would like to make a few general

announcements.

Transcripts of today's meeting will be available from Free State Court Reporting, Incorporated.

Information on purchasing videos of today's meeting can be found on the table outside the meeting room.

Handouts of today's presentation are available at the registration desk.

The press contact for today's meeting is Deborah Kotz.

I would like to remind everyone that members of the public and the press are not permitted in the panel area, which is the area beyond the speaker's podium. I request that reporters please wait to speak to FDA officials until after the panel meeting has concluded.

If you would like to present during today's Open Public Hearing session, please register with James Clark at the registration desk.

In order to help the transcriber identify who is speaking, please be sure to identify yourself each and every time you speak.

Finally, please silence your cell phones and other electronic devices at this time.

Dr. Talamini.

DR. TALAMINI: Thank you, Lieutenant Commander Garcia.

I just wanted to give Dr. Afifi the opportunity to introduce himself all the way from the West Coast.

Dr. Afifi.

DR. AFIFI: Sorry, I walked from California.

(Laughter.)

DR. AFIFI: I am a professor emeritus in the School of Public Health at UCLA. Thank you.

DR. TALAMINI: Thank you.

We will now proceed to the Sponsor's presentation.

(Off microphone comment.)

DR. TALAMINI: Oh. In addition, we have one Panel member unable to get here due to the weather who is on the phone, I think. Could she please introduce herself for us?

DR. FAULX: Can you hear me?

DR. TALAMINI: Yes, just barely.

DR. FAULX: Okay, thanks. I'm Ashley Faulx. I am an Associate Professor of Medicine at University Hospital at Case Medical Center and at the VA in Cleveland, and I am a therapeutic endoscopist specializing in GI cancers.

DR. TALAMINI: Thank you, Dr. Faulx.

We will now proceed to the Sponsor's presentation. I would like to invite the Sponsors to approach the podium.

I will remind public observers at this meeting that while this meeting is open for public observation, public attendees may not participate except at the specific request of the Panel Chair.

The Sponsor will have 75 minutes to present.

By way of process for the Panel members, following this hour and 15 minutes we will have a 30-minute opportunity, as Panel members, to ask clarifying questions, and those are usually the best form of question for that period. If there are aspects of the presentation

that you don't understand clearly or that you need clarified, that is the ideal time to do it. So during the presentation, please jot down any things that are not clear to you or clarifying questions that you want to get answered, and following the Sponsor's presentation, we'll have 30 minutes to do that.

So with that said, Sponsors, the podium is yours.

MR. RASMUSSEN: Good morning, Mr. Chairman, members of the Committee, FDA colleagues, and all participants here today. My name is Tom Rasmussen, and I'm Senior Director of Clinical and Regulatory Affairs for ASTORA Women's Health. ASTORA is pleased to be here today to share the results of our IDE study that investigated the efficacy and safety of the TOPAS system for women suffering with fecal incontinence.

TOPAS is a new, innovative, and minimally invasive approach for women living with fecal incontinence, also known as FI. The TOPAS system uses surgical mesh to safely support a woman's natural anatomy, and it has been shown to reduce episodes of fecal incontinence and improve a patient's quality of life. Importantly, the TOPAS system is not placed transvaginally, as compared to the mesh implants used for urinary incontinence and vaginal prolapse.

Fecal incontinence is a debilitating condition that causes shame, embarrassment, depression, poor self-esteem, and self-imposed social isolation. Women suffering with FI have an inability to control bowel movements, causing stool to leak unexpectedly. It can range from an occasional leakage of stool while passing gas, to a complete loss of bowel control. There is no universally accepted definition for what is considered mild, moderate, or severe fecal incontinence. But on a week-to-week basis, typical patients will experience

multiple episodes of FI.

There is no one treatment option that works for all patients. Successful reduction in FI episodes does not necessarily eliminate the need for concomitant treatment such as medications to control stool consistency. And some therapies could result in additional clinical burdens such as complex device management, surgical revisions, and device replacement.

TOPAS offers a therapeutic option that differs in potential mechanism of action in implant location. Although the mechanism of action for TOPAS is not completely understood, we believe that TOPAS works by providing support to the anorectum to compensate for loss of pelvic floor muscle function as a result of degradation in muscle tone or damage from obstetric injury.

Let's review the placement of the TOPAS device, which is positioned inferior to the anorectum and parallel with the puborectalis. Unlike transvaginal mesh, which sits very close to other organs like the vagina and bladder, the TOPAS mesh sits approximately 2 cm away from the anorectum. Intervening tissues include fat and the sphincter muscles.

The following animation provides an overview of the TOPAS implant procedure. Please note that frequent glove change, shown by the changing glove color, is required when moving between the anus and the vagina.

The TOPAS system has two stainless steel insertion needles and a reinforced Type I polypropylene mesh which is covered with a removable plastic sheath. This helps reduce friction during delivery. What's critical on this procedure is where and how the mesh is placed. Unlike transvaginal mesh, the TOPAS system does not involve the vagina. Instead,

two incisions are made in the thighs and buttocks. A post-anal tunnel is made between the two buttock incisions to create a space for the mesh to lie flat. Then the mesh assembly is pulled through this tunnel. The needle is passed from the left thigh incision through the ischiorectal fossa to the rectum and out through the buttock incision. The end of the sheath is then pulled through the thigh incision. The same procedure is then carried out on the patient's right side. The mesh is then tensioned by pulling upward with a finger in the rectum until slight tension is felt. The polymer sheath is removed, the mesh is cut, and the thigh and buttock incisions are closed.

The average time to complete a TOPAS implant is 33 minutes. The mean blood loss was 13 cc with no transfusions. And immediate post-procedure pain was 3.2 on a scale of 0 to 10.

The TOPAS device is intended to treat women with fecal incontinence, also referred to as accidental bowel leakage, who have failed more conservative therapies. Patients may have tried dietary change or medications or pelvic floor muscle training, all with limited success in reducing their number of FI episodes.

Let me describe our clinical development program. ASTORA engaged physician and statistical experts in developing a clinical program. The result was a single-arm, adaptive design study that required a minimum of 152 patients with symptomatic fecal incontinence who would be assessed for efficacy and safety. A premarket approval application for TOPAS was submitted to the FDA on April 17th, 2014. The TOPAS system is not commercially available in any country. ASTORA recognizes that the highest level of evidence for medical device approvals are randomized controlled trials. However, federal regulations do allow

the use of valid scientific evidence from objective trials without matched controls. The TOPAS single-arm study provides such evidence to determine if there is reasonable assurance of the safety and effectiveness under its condition of use.

Today we will present data that will show that the TOPAS clinical study significantly exceeded its primary endpoint. This endpoint required that more than 50% of the study participants achieved at least a 50% reduction in the number of fecal incontinence episodes. In fact, 69% achieved the primary efficacy endpoint, and this observed reduction was durable over a 3-year follow-up period. Moreover, the TOPAS clinical study demonstrated improvements in important and clinically relevant quality of life measures.

We will also present data showing that TOPAS demonstrated a favorable mesh safety profile. It's important to understand that TOPAS is not placed transvaginally, but is placed posterior to the anorectum and parallel to the puborectalis. There were no reported organ perforations. And in the 509 patient-years of follow-up, to date, we have not observed complications such as erosions, extrusions, bowel obstructions, device revisions, or unanticipated adverse device effects.

We will show you today that TOPAS significantly reduces FI episodes and increases the quality of life in patients who have FI.

Here's our agenda. Dr. Mikio Nihira of the University of Oklahoma College of Medicine will discuss the significant impact of FI and the need for new, safe treatment options. Dr. Dee Fenner of the University of Michigan will outline our clinical study design, summarize the efficacy of TOPAS, and will provide a clinical perspective. Dr. Nihira will return to review the TOPAS safety data. Paul Below from ASTORA will review the physician

education program and describe our postmarket activities. He will also serve as our moderator for Q and A.

In addition, the following experts are with us today to help answer any questions, including Dr. Massarat Zutshi from the Colorectal Surgery Department at the Cleveland Clinic Foundation, and Andy Mugglin, statistical consultant for ASTORA. All of our external presenters have been compensated for their time and travel expenses.

I would like now to introduce Dr. Mikio Nihira.

DR. NIHIRA: Thank you, Tom.

My name is Mikio Nihira, and I am a Professor of Obstetrics and Gynecology and Geriatrics at the University of Oklahoma, and I am an investigator in the TOPAS clinical trial. I have been involved in the surgical care of women with fecal incontinence for the last 20 years and have participated in several studies evaluating new techniques for the treatment of fecal incontinence. I appreciate the opportunity to discuss the unmet medical needs of this patient group. I have seen the toll these problems have on patients and the impact on their quality of life.

Today I will discuss the pathophysiology of fecal incontinence, a condition that is undertreated and on the rise in the United States. I will also present its consequences on patients and the available treatment options.

Let's begin with the pathophysiology of the disease. There are several mechanisms that are important for normal fecal continence. This slide lists three of these mechanisms. The first relates to innervation and correctly controlling rectal sensation. Next is that the pelvic floor and sphincter muscles are undamaged and working properly. You also need

proper stool consistency, meaning that the stools are not so soft that the sphincter is unable to hold them or too hard so that they are difficult to pass. Disruptions to any one of these mechanisms can lead to fecal incontinence.

So what can cause these dysfunctions? There are potentially several contributing factors. Fecal incontinence can be caused by a combination of congenital, anatomic, neurologic, and functional abnormalities. These may have resulted from obstetric trauma, age, diarrheal states, inflammatory bowel disease, and neurological conditions like diabetic neuropathy or multiple sclerosis. Patients may have one or several of these factors, which makes it difficult to identify the primary cause of their fecal incontinence.

And adding to the complexity is that while there are several ways to characterize fecal incontinence, the available diagnostic tools may not be helpful to delineate the pathophysiology or potential treatment responses. For example, just because a patient with fecal incontinence may demonstrate a sphincter defect on ultrasound, this doesn't mean that the defect is the primary cause of her fecal incontinence. Additionally, it does not correlate well with the severity of symptoms or reveal which treatment will be most efficacious.

At the same time, fecal incontinence is a condition on the rise in the United States. As many as 10% of community dwelling women suffer from fecal incontinence at least once a month. It is estimated that nearly 11 million women are currently affected by fecal incontinence. With our aging population, it's expected that this number will grow with time.

In addition to the broad impact on the population, fecal incontinence also has a

debilitating effect on an individual's quality of life. Women with fecal incontinence often find that their symptoms limit their lifestyle, activities, ability to work, and personal relationships. Research shows that women with fecal incontinence are embarrassed with their condition and are at increased risk of depression. They often plan their daily activities around access to a bathroom. With fecal incontinence, women can't just put on a pad and continue their day after an accident. As a result, they avoid going out in public, which results in social isolation. In fact, fecal incontinence can be one of the most psychologically and socially debilitating conditions in an otherwise healthy woman.

When it comes to treatments, there is a lack of knowledge about available options among patients and providers. Not surprisingly, the stigma surrounding fecal incontinence can create barriers to successful management. Women are often too embarrassed to seek medical help and attempt to manage their condition on their own in secrecy. In fact, published literature shows that fewer than 3 in 10 women report the condition to their healthcare providers. When women do get treatment, options have various risks, benefits, and efficacy profiles, and no one approach has been found to work for everyone.

Treatment options range from nonsurgical options to major surgical interventions. The conservative approach includes changes in diet, medications, and pelvic floor muscle training. If patients don't respond to a conservative therapy, they can then proceed to minimally invasive interventions. These include an injectable bulking agent and sacral neuromodulation, both of which were approved in 2011. In addition, there are more invasive surgical options such as sphincter repair or colostomy. Sphincter repair can be done at any time to treat a localized injury in the sphincter muscle. Diversion with a

colostomy is usually performed as a last resort and has poor patient acceptance.

Thinking about the patients who have failed conservative therapy, let's review in more detail the possible device options. This table lists the two devices I just discussed as well as two others, a vaginal insert and a magnetic sphincter augmentation device. These were FDA approved in 2015 but have not been utilized outside of clinical trials in the United States.

What we see across the device spectrum is that most require ongoing device maintenance, half are incompatible with an MRI, and most are limited in their commercial availability to physicians and patients.

Understanding these gaps and the resulting unmet need, patients deserve new and accessible treatment options to address this debilitating condition. The ideal therapy should be efficacious, safe, minimally invasive, and low maintenance, while improving patients' lives.

Thank you. And I now invite Dr. Dee Fenner to present the study design and efficacy results.

DR. FENNER: Good morning. My name is Dee Fenner, and I am the Furlong Professor of Women's Health and Director of Gynecology at the University of Michigan, and I am a study coordinating investigator for the TOPAS clinical trial. I'm board certified in female pelvic medicine and reconstructive surgery. I have been taking care of women with FI and other pelvic floor disorders for over 20 years. I manage these patients both medically and surgically as part of a large multidisciplinary team at the University of Michigan. I have published over 100 peer review publications in the area of pelvic floor

disorders. I am a firm believer in the use of native tissue for the treatment of pelvic organ prolapse.

On behalf of the study investigators, I am pleased to present the study design and efficacy results for the TOPAS system. The data that you will see today demonstrates that the treatment effect with TOPAS is immediate, consistent, durable, and is making positive changes in patients' lives.

The clinical study evaluated the long-term efficacy and safety of the TOPAS system for treating fecal incontinence in women who had already tried and failed conservative treatment options. This clinical trial was a prospective, single-arm, open-label, multicenter study. There were 15 centers in the United States. Eight centers were led by colorectal surgeons, and seven were led by urogynecologists.

ASTORA consulted with a multidisciplinary study advisory committee, and the FDA and determined that a single-arm, open-label design where patients served as their own control was the most appropriate model for several reasons. First, the committee concluded that randomization to conservative therapy was inappropriate, since the study only enrolled patients who had already failed these treatments. Next, randomizing to another device was not an option, since no comparable FDA-approved device for treating fecal incontinence was available at the time the trial was initiated. While we considered a sham control, the committee determined that the benefits did not outweigh the risks, and subjecting patients to unnecessary anesthesia and incisions. Finally, as you heard earlier, this design met FDA's standard for valid clinical evidence.

Let's discuss how we selected our sample size. In order to determine the success of

the TOPAS trial, we first had to determine our primary outcome. We defined a responder as someone who achieved at least a 50% reduction in FI episodes from baseline. This is a standard definition of treatment success that has been used when evaluating the efficacy of other fecal incontinent treatments. Study success is achieved by demonstrating that the response rate is greater than 50%, and this is the success criterion that has been used in recent clinical trials for FDA approval of FI devices.

Throughout this presentation, we will refer to those who met this objective treatment as responders.

When it came to estimating the rate of treatment responders, there was little data about the potential efficacy to guide us in sample size calculation. Because of this, the clinical trial applied a two-stage adaptive design that allowed for a planned sample resize estimation between stages for efficacy.

A total of 152 patients were initially planned for the TOPAS study across two stages, 80 in Stage I followed by at least 72 patients in Stage II. Sample size re-estimation took place once Stage I patients reached their 12-month follow-up. Treatment response in the first 80 patients confirmed that the original sample size estimates were appropriate and did not require a re-estimation. Once Stage I and Stage II patients completed their 12-month follow-up, the study data were analyzed. There were no differences between the stages in terms of demographics and baseline characteristics. The full details of the methods used to determine power calculations and sample size are outlined in the Panel pack.

Following the TOPAS procedure, patients had a specific follow-up schedule with their surgeons. At each of these visits, physicians performed a physical exam to assess for

adverse events. Patients returned their 14-day bowel diary, and they completed a series of validated health questionnaires, which I will detail later. Unscheduled visits could occur at any time to evaluate adverse events.

This is a sample of what the 14-day bowel diary looks like. ASTORA worked with study investigators to develop this diary, which is similar to the ones used in clinical practice and FI research. The number of fecal incontinent episodes a patient recorded over a 2-week period was used to determine our major efficacy outcome.

The primary efficacy objective was to demonstrate that more than half of the study participants could achieve at least a 50% reduction in fecal incontinent episodes from baseline to 12 months.

For our primary endpoint at 12 months, the responder rate was calculated with missing data considered as treatment failure. For long-term follow-up, we will present data as observed case scenario, calculated with the exclusion of missing data.

With our single-arm design, showing sustained results was a key factor to demonstrate efficacy. So our secondary objectives focused on long-term durability of efficacy, whether there was a reduction in incontinent days, urge episodes, and symptom severity, whether there was an improvement in disease-specific quality of life, and a quantification of pelvic floor distress and impact to sexual function.

The TOPAS study also had a comprehensive safety objective to summarize all adverse events, specifically to quantify both pelvic pain and known complications of surgical mesh used in pelvic floor reconstruction.

There were several measured inclusion criteria in the study. All participants had to

be 18 years or older and have tried and failed at least two different conservative therapies. Women also had to have FI for at least 6 months and experience at least four episodes in a 14-day period. Women over 50 years of age also needed to have met the colon cancer screening guidelines.

Participants were not allowed to participate if they were pregnant or planning a future pregnancy, if they had been diagnosed with an inflammatory bowel disease, if they had chronic watery diarrhea, or if they had a history of recent gynecologic or gastroenterologic surgical repair procedures. The full set of exclusion criteria is listed in your Panel pack.

Now, let's turn to the study results: 207 patients signed the informed consent agreement and enrolled in the study; 55 patients exited prior to implant, the majority of whom did not meet the inclusion criteria or declined further participation; 152 patients received the TOPAS implant, and 20 patients discontinued prior to the 36-month visit due to declining further participation, lost to follow-up, or receiving a neuromodulator implant; there were 2 non-treatment-related deaths, both due to cancer; 132, or 87% of patients, were still active in the study at the 36-month visit.

The TOPAS study population is representative of women with fecal incontinence who seek treatment. Study participants had a mean age of about 60 years, and the youngest patient was 32 years old. Most had been living with fecal incontinence for an average of 9 years. The group was largely Caucasian and had a mean BMI of 27.8. The median number of FI episodes among study participants was 18 during a 14-day period. The etiology in most patients was due to obstetric trauma, although there was a large number of patients

for whom the etiology was unknown.

This table shows that a large percentage of participants had a history of other pelvic floor disorders. As part of the inclusion criteria, all of these women failed two conservative treatments, and in fact, 40% had tried and failed all three.

Now, let's review the efficacy results. The TOPAS study met its primary efficacy endpoint of reducing FI episodes at 12 months. This was calculated using the most conservative method, which counted missing patients as treatment failures. As I mentioned earlier, because this was an adaptive design, each stage of the study was conducted and analyzed independently.

We met our primary efficacy objective at Stage I with 65% of women experiencing at least a 50% reduction in fecal incontinent episodes from baseline to 12 months, with a p-value of 0.0048. We met the primary objective again in Stage II with a 74% treatment success rate with a p-value of less than 0.0001. These independent stages demonstrate that the response rate of patients was reproducible. Overall, 69% of study participants achieved at least a 50% reduction in fecal incontinent episodes from baseline.

This graph shows the median number of fecal incontinent episodes for 14 days on the y-axis, with the 25th and 75th percentiles noted in the error bars. Note that there was a 72% reduction in the median number of episodes from baseline to 3 months, and this reduction was sustained throughout the study.

This is the completed visits responder rate over time. At 36 months, 20 women had discontinued in the study, and 108 reached their 36-month visit. At 12 months, 72% of patients had at least a 50% reduction in fecal incontinent episodes. This percentage

remained stable across 36 months.

In another analysis where we assumed that all missing data were non-responders, we find the responder rate is 58% at 36 months. Again, with this worst-case scenario, the study achieves its primary endpoint.

While success was defined with at least a 50% reduction in FI episodes, we also looked at different improvement categories from baseline. Twelve percent of women reported a worsening of their FI, and 7% found no change, most of which was due to missing data. Eighty-one percent of women noted some improvement in FI episodes. At 12 months, 42% had at least a 75% reduction in FI, and 19% had complete continence.

We also looked at efficacy at 12 months by subgroups to determine whether there are particular factors that influence or determine the outcome. This forest plot shows a few of the factors we analyzed. A complete list is included in your Panel pack. We did not find that any one factor predicted that a patient would be a responder.

Here we see the median number of incontinent days across the study. The median decreased from 10 incontinent days at baseline to 4 days at the 3-month follow-up. In other words, patients reduced by 60% the number of incontinent days. This reduction was sustained through 36 months.

This graph demonstrates the improvement in urge episodes. An urge episode was defined as the patient was suddenly aware and rushed to the toilet but still had an accident. These urge episodes went from a median of 4 at baseline to 0 at all follow-up visits.

Importantly, we also saw improvement in quality of life. We heard earlier about the negative impact fecal incontinence has on patients' lives and how it can affect everything

from a woman's self-esteem to her ability to go to work.

This is a summary of all quality of life assessments used in the study. Two of these instruments, the Pelvic Floor Distress Inventory and the Pelvic Floor Impact Questionnaire, also have subscales that specifically address colorectal function. These assessments were pre-specified as descriptive endpoints in the analysis plan. Therefore, no statistical significance was calculated. All of the assessments showed an improvement in quality of life, except for the sexual function questionnaire, which showed no impact. Each instrument is detailed in your Panel pack. But to provide a few illustrative examples, let's review results from all of the disease-specific instruments.

The Wexner symptom severity scoring system measures the type and frequency of incontinence, pad usage, and lifestyle alteration. A reduction in score indicates an improvement in a patient's FI symptoms.

This is an example of a severe patient with a score of 15. After TOPAS, the same patient went to a score of 9. This scale has not been evaluated in a non-FI population. I find that most parous women rarely score 0, and scores of 2 to 6 are common in women who do not self-identify as having FI.

In the TOPAS study, the mean Wexner score decreased from 13.9 at baseline to 9.4 at 3 months and remained below 10 through the 36-month visit, consistent with reductions in both fecal incontinent episodes and incontinent days. Looking from baseline to all follow-up visits, we observed a significant improvement in the Wexner score. More importantly, in my practice, I would view this reduction as a clinically meaningful improvement.

This is the fecal incontinence quality of life score measured on a 1 to 4 point scale. Over a 36-month period, a higher FIQoL score indicates a better quality of life. The validated FIQoL scale showed that patients experienced significant improvement across all four domains that it measures: lifestyle, depression, embarrassment, and coping skills. Again, improvements seen at 3 months were sustained through the 36-month visit.

We also looked at how these scores correlated with a patient's treatment response, and what we found is that the higher the response rate, the greater the improvement in quality of life domains.

This forest plot looks at the FIQoL domain of embarrassment, which we just saw on the last slide. The y-axis is the response rate, with the red line indicating the accepted 50% reduction in FI episodes as the definition of success. Patients who achieved at least a 50% response saw greater improvements in this quality of life measure, again supporting the use of our primary endpoint as a meaningful outcome. The other domain showed similar correlations with treatment response. And these analyses can be found in your Panel pack.

The last two quality of life instruments I will review are the colorectal-anal subscales of the Pelvic Floor Distress Inventory and the Pelvic Floor Impact Questionnaire. A few example questions from both are listed here, such as:

- Do you usually lose stool beyond your control if your stool is loose or liquid?

  and

- Does your FI usually affect your ability to do household chores?

The subscales are scored on a 0 to 100 scale, with lower scores indicating less colorectal-anal distress or patient impact. Most notable, the minimal clinically important

difference, or MCID, values have been established for both subscales. For the Colorectal-Anal Distress Inventory, we saw a mean decrease of at least 20 points at all follow-up visits, which is four times the MCID established for this questionnaire. For the Colorectal-Anal Impact Questionnaire, we see over the entire study period at least a 27-point improvement in quality of life, which exceeded the MCID by 3.5 times.

We also looked at self-reported health resource utilization as another way to assess the patient as well as societal impact. From baseline to 36 months, patients decreased their use of diapers or pads by 50%. There was a 94% decrease in the number of healthcare provider visits, and patients reduced the number of days they had to take off work by 86%.

Patient-reported outcomes as key indicators to the utility of surgery. Although the surgical satisfaction survey was only offered on a one-time basis to all active participants between 3 and 36 months postoperatively, it provides valuable insight into the patient's perception of benefit and risk. Eighty-six of the 152 patients replied to this voluntary questionnaire, and overall 80% said they would have the surgery again and would recommend it to someone else.

In summary, the TOPAS study met its primary efficacy endpoint. We showed that 69% of women experienced at least a 50% reduction in fecal incontinent episodes from baseline. We also saw positive changes in all of the secondary efficacy objectives. There were sustained decreases in fecal incontinent episodes, indicating long-term efficacy through 36 months. We saw decreases in FI urge episodes and incontinent days starting at the 3-month follow-up visit. And we saw both consistent and clinically important improvements in patient-reported symptom severity and quality of life. The study showed

that the treatment effect with TOPAS is immediate, consistent, durable, and positively changes patients' lives.

Thank you. I now invite Dr. Nihira to the lectern to present safety data.

DR. NIHIRA: Although I've been treating pelvic floor disorders, such as fecal incontinence, for 20 years and have witnessed the progression of less morbid treatment options for women, I have always witnessed the complications that have been associated with surgical procedures utilizing mesh to treat pelvic organ prolapse and urinary incontinence.

Today I will present safety data from the TOPAS clinical study. This data supports that the placement of the TOPAS mesh results in a different safety profile than meshes that are placed transvaginally. I will briefly review important components of the implant procedure, the study safety objectives, how we collected data, as well as all treatment-related adverse events, serious adverse events, and adverse events of special interest.

Due to its anatomical placement, TOPAS has a unique mesh safety profile. To review, the TOPAS system is inserted lateral to the levator ani muscle and inferior to the anal sphincter. After its placement, there is an approximately 2 cm tissue buffer between the mesh and the anus, and because of this placement, the potential for mesh erosion into the anus or rectum is reduced. Since the placement of TOPAS does not require transvaginal incisions, there is a lower direct risk of vaginal erosion.

The data demonstrate that TOPAS has a favorable safety profile. In 509 patient-years of follow-up, there have been no erosions into the vagina or rectum, extrusions through the incisions sites, perforations into the vagina, bowel, or bladder. In addition,

there were no bowel obstructions. There have also been no device revisions or unanticipated adverse device effects reported.

The study safety objective was to characterize the safety profile of TOPAS. To do this, ASTORA systematically collected all adverse events. Mesh-related complications were specified in the protocol and brought to the attention of all investigators as part of the mandatory training that physicians received prior to performing the procedure. These events included erosion, extrusion, infection, pelvic pain, leg pain, and dyspareunia.

To monitor for these events, the protocol required a physical exam at every follow-up visit and required study surgeons to confirm that the surgical incision sites were intact. Investigators were also required to question the patient on whether they had any potential adverse events since their previous visit. In addition, patients were required to report potential adverse events to the study center between visits. Regardless of when a patient reported a potential adverse event, standard of care diagnostics were performed to guide treatment.

Once an adverse event had been reported by the site, it was reviewed and adjudicated by an independent committee to determine the seriousness and whether it was related to the device, the procedure, or both. This expert panel is comprised of Dr. Rebecca Rogers, a urogynecologist; Dr. Satish Rao, a gastroenterologist; and Dr. Anthony Senagore, a colorectal surgeon. In monitoring the overall study safety and conduct of the study, the adverse events adjudication committee members were joined by statistician William Thomas and patient advocate Nancy Norton.

Now, let's review the results. A total of 677 adverse events were reported among

the 152 patients who received the TOPAS implant. The adverse events committee determined that 115 events were treatment related. As a reminder, these included both device- and procedure-related events. Of these events, 8 were determined to be serious. No one withdrew from the study due to a treatment-related adverse event. There were no unanticipated adverse device effects and no treatment-related deaths. This presentation will focus on those 115 treatment-related events. Details of all other events are in your Panel pack.

Let's take a look at the most common of these events. Overall, the majority of the 115 treatment-related adverse events in the study were not judged to be serious and resolved without reported sequelae. At the request of the data monitoring committee, treatment-related adverse events were aggregated for analysis.

All pelvic area pain events included any pain event between the navel and the knee. This infection category was broad and ranged from incision site infections to bladder infections. Urinary problems ranged from urinary retention to urinary incontinence. Pelvic organ prolapse included rectal and vaginal prolapse; it is important to keep in mind that women with pelvic floor disorders, such as fecal incontinence, may have other preexisting pelvic floor disorders such as urinary incontinence and pelvic organ prolapse. Four patients had defecatory disorders; two were episodes of constipation that were diagnosed within 5 days of the procedure and were resolved within 10 days; the remaining two events were cases of worsening fecal incontinence that remain ongoing. The "Other" category included items such as posttraumatic stress disorder, deep vein thrombosis, and headache.

I will talk more about these categories of adverse events of special interest in a few

minutes. But first I will briefly describe the general characteristics of treatment-related adverse events along with serious adverse events.

The majority of events were short in duration and lasted 30 days or less. The median duration was 25 days. Eighty-one percent of events were resolved. And of the unresolved events, the majority consisted of pelvic area pain, pelvic organ prolapse, and urinary problems.

When assessing the status of adverse events, resolution of event is determined by a combination of patient reporting and physician assessment. When an event has been determined to be resolved, a duration is calculated based on the date of onset to its resolution. Ongoing events included those in patients who are still active study participants. It also includes events in patients who have exited the study as per the recommendations of our data monitoring committee, which means that their status remains unresolved until study closure. In both of these cases, the duration continues to accumulate until event resolution.

Ninety-two percent of the adverse events were managed without treatment or were addressed with nonsurgical interventions such as medication and physical therapy. Nine events required surgery, and six of these were related to preexisting conditions, which are listed here. The remaining three cases were de novo pelvic organ prolapse, which I will talk about more in just a few slides.

Moving on to serious adverse events, there were eight treatment-related serious adverse events; none were life-threatening. Four of the serious adverse events were related to preexisting conditions. These included one case of posttraumatic stress disorder

that occurred 1 week before the patient received the TOPAS device, one case of chronic obstructive pulmonary disease exacerbation, one case of worsening sciatica pain, and one case of worsening pelvic organ prolapse. The remaining four serious adverse events included one case of deep vein thrombosis, one case of MRSA infection of the left hand, and two de novo pelvic organ prolapse cases. With the exception of the case of PTSD, which is ongoing, all serious adverse events were resolved without reported sequelae.

Now, let's return to pelvic pain. In total, there were 50 pelvic area pain events observed in 28% of the total population. The median duration of these events was 88 days. Included with this range are nine events that are ongoing. The majority resolved. One pelvic area pain event required surgery. This was the previously mentioned case of worsening sciatica. Therefore, 98% of these events required either no or nonsurgical interventions. Of the cohort of patients who experienced pelvic pain, 67% achieved treatment success as of their last study visit and recorded improvements in quality of life measures.

We also looked at pain severity. We assessed pain severity using the pain rating instrument shown here. Patients completed this assessment at each study visit through 12 months. This scale rated pain between 0 and 10, with 0 meaning there was no pain and 10 being the worst pain possible. For those patients who had an adverse event of pelvic area pain, the mean pain score at baseline was 0.5. When looking at the last available recorded pain score for these patients, the mean score was only slightly higher.

When we analyze patients whose pain lasted more than 120 days, there are a total of 21 prolonged pain events in 18 patients. These patients had a mean severity score of 0.8

at baseline, and using their last available pain data up through 12 months, had a mean pain score that remained in the mild range at 2.1.

After 12 months, pain was assessed with one question of the PFDI. Sixty-seven percent of patients, of the 18 patients with prolonged pain, reported that they did not usually experience pain or discomfort in the lower abdominal or genital region. Nine of these patients had resolution of their symptoms. Their pain lasted a mean of 368 days. The remaining nine patients include five who have exited the study, and their pain status is unknown. The four that are still actively participating in the study are continuing to be monitored.

I will now move on to other events of special interest, beginning with infection. Twenty-five infection adverse events all resolved without reported sequela. Nine were incision site infections where the criteria was quite liberal and included any investigator perception of redness that was associated with a treatment such as an antibiotic. Two of the infections were abscesses. Both were superficial and highly localized to the surgical incisions. The 14 other events included events such as fungal infection of the skin, urinary tract infections, and MRSA of the left hand. All infections were treated nonsurgically and had an average duration of less than 30 days.

Urinary problems were infrequent, and the cases we observed are listed here. The urinary retention cases all occurred immediately post-procedure and resolved within 2 days of onset. The majority of the urinary incontinence cases were reported worsening in symptoms that occurred within the first year of implant. Three of the four cases remain ongoing. The dysuria event was attributed to catheterization during the procedure and was

resolved within 2 weeks.

The adverse event of pelvic organ prolapse included rectal and vaginal prolapse. And as a reminder, women with pelvic floor disorders, such as fecal incontinence, may have other preexisting pelvic floor disorders such as prolapse. There were 13 events of prolapse in nine patients. The five cases of recurrent prolapse occurred in four patients, of which all had a history of prolapse prior to enrolling in the study. The eight cases of de novo prolapse occurred in seven patients. Because chronic straining is a proposed cause of prolapse, we scrutinized the data for all of these patients and concluded there were no associated adverse events of increased fecal retention or straining.

In considering the treatment-related adverse events, it is important to recognize that these events did not preclude a patient from experiencing benefits. When looking at the fecal incontinence quality of life scores, patients with treatment-related adverse events experienced improvements from baseline. Eighty-two percent reported improvements in lifestyle and embarrassment, and 80% reported improvements in coping and depression. At 12 months, those who experienced an adverse event achieved a 65% responder rate, which was similar to the 73% responder rate in those who did not experience an adverse event.

As the final category of adverse events of special interest, we have not observed any cases of erosion, extrusions, perforations, or organ obstructions.

Before I conclude, in response to questions from FDA regarding possible cases of mesh erosion or obstructions, ASTORA conducted a thorough review. This included interviewing the treating surgeons and collecting all available medical records, which confirm that repeated vaginal and rectal examinations were performed on this cohort of

patients. This information was supplied to the adverse events adjudication committee, who reviewed all of the evidence and concluded there were no cases of erosion or obstruction.

In summary, based upon the data from this clinical trial, TOPAS is well tolerated and offers patients a safe treatment option where the observed adverse events were manageable. The majority were short in duration, mild, and resolved without reported sequelae. There were eight serious adverse events, and 92% of the treatment-related adverse events were managed without therapy or received nonsurgical treatment.

I'm now happy to ask Mr. Below to the lectern to review the company's physician training and post-approval study plan.

MR. BELOW: Hello, my name is Paul Below, and I am a principal clinical research specialist at ASTORA.

At ASTORA, we are committed to providing efficacious and safe therapies for women living with pelvic health disorders, and physician education is a critical component to this mission. For TOPAS, we've designed a comprehensive and robust education program to help physicians achieve the best possible patient outcomes. This program is modeled after the successful training curriculum we used in the TOPAS clinical study as well input from our physician advisory committee. This program addresses the disease state, the relevant anatomy, patient selection, and procedural requirements to help physicians use the TOPAS system safely and effectively

Highly qualified physicians will be admitted into the program. There are three required qualifications, which include those who are board certified in female pelvic medicine and reconstructive surgery or colon and rectal surgery, and those who are

currently treating FI, and lastly, those with surgical experience implanting other FI devices or mesh in the pelvic floor.

Our training program includes three phases:

1. An e-learning introductory course;
2. A classroom didactic course with a hands-on component; and
3. A practical surgical experience overseen by a qualified proctor.

Let me now describe the program. The first phase of the training includes seven e-learning modules and provides a framework for the treatment of fecal incontinence and how TOPAS can fit into a patient's treatment plan. The curriculum will focus on fecal incontinence and its etiology. It will also include a special section on pelvic anatomy and physiology, since this knowledge is critical to understanding how to conduct a TOPAS procedure.

Trainees will also receive product information, including instructions on the implant procedure and considerations on how to manage potential complications. Trainees must demonstrate understanding of the material by passing a test at the end of each module before advancing to the next phase.

In the second phase, the objective is to get the physicians comfortable with the device and the actual implant procedure. This 1-day course will be conducted at regional centers by faculty highly experienced with the TOPAS procedure. This phase provides additional didactic training, including a review of the e-learning modules and case studies that will focus on patient selection and managing complications. This is followed by a hands-on experience implanting the TOPAS device in a pelvic model and in cadavers.

During Phase 3, trainees are evaluated by a qualified physician/proctor on their ability to perform all steps of the TOPAS implant procedure. Two proctored cases will be required for all trainees. This requirement is based on our experience with successful proctoring in the TOPAS clinical study and is also based on input from our physician advisory committee. Once this final step is completed, physicians will receive a record of training completion from ASTORA. It is our expectation that trainees will maintain their expertise with the use of the TOPAS system.

So ASTORA will provide ongoing support to TOPAS-trained physicians, including a refresher course. The refresher course will include a repeat of the e-learning modules and the pelvic model hands-on training, with an additional option of cadaver training and proctoring upon request. This course will be available to all trainees but will be required for those who have not completed at least eight TOPAS cases annually.

In addition, we will maintain a multidisciplinary physician committee to advise TOPAS implanters on managing specific complication cases. We will continue to collaborate with our physician advisors and the FDA to ensure that this training program is rigorous. With the proper training, the TOPAS system can be used safely and effectively, leading to improvement in the quality of life for women with FI.

ASTORA is also committed to the ongoing monitoring of the product upon market release. It is proposing a comprehensive, proactive, long-term surveillance program to monitor the safety and performance of the TOPAS device. To accomplish this, we designed a two-part postmarket plan to complement and augment our regular complaint handling program.

The first part of this plan is the expansion of the TOPAS clinical study to 5 years of follow-up. The second part is the creation of a new enrollment study that will evaluate the safety of patients implanted with the TOPAS system post-approval. This two-part plan will enable us to monitor for known mesh safety issues that Dr. Nihira described earlier.

Let's first talk about the extension of the TOPAS clinical study. Extending the study out to 5 years of follow-up provides us with a rigorous way to collect long-term safety data in a clinical trial setting. Since December 2013, when we received FDA approval for this extension, we've been implementing this program at the investigational sites. We will continue providing the Agency annual updates on safety and efficacy until the study is completed in early 2018.

As discussed earlier, this safety program includes monitoring all adverse events, with a special focus on mesh-related complications. This also includes a long-term safety endpoint to demonstrate that the proportion of patients experiencing at least one treatment-related serious adverse event is lower than 25% at 60 months of follow-up. It also includes the addition of a digital rectal exam, to be conducted at the long-term follow-up visits, in order to detect rectal erosion, possible rectal erosion. All other assessments of performance, including the collection of data from patient bowel diaries and quality of life questionnaires, will continue.

In addition to extending the pivotal study, ASTORA is designing a new post-approval study that will enroll a new cohort of patients. ASTORA submitted a draft proposal for this new study to the FDA in July of last year, which is detailed in their Executive Summary. The primary study objective will focus on safety. We look forward to continuing to work with

the FDA after this panel meeting to refine the study design and to determine the study endpoints, estimate the number of subjects and study centers, and the need for a control or comparator arm.

Regardless of the final study design, ASTORA agrees with FDA that the following elements should be included in the new post-approval study. These include the collection of additional information in the patient bowel diary, such as the occurrence of straining, constipation, and pain during defecation; an assessment of pelvic organ prolapse at baseline and throughout the study; detailed assessment of pelvic pain to measure the nature of the pain intensity, location, and etiology; and additional imaging techniques to study changes in the anorectum with TOPAS placement.

In summary, ASTORA is committed to this two-part plan, which will continue to monitor long-term surveillance of the TOPAS system through both the extension of our clinical study and the conduct of a new post-approval study. Upon market release, ASTORA will be conducting a limited launch of the TOPAS system. Initial product use will be limited to previous TOPAS study implanters and to investigators in the new post-approval study. We believe this is a comprehensive plan to monitor safety and performance of the device.

Through the physician education and post-approval program, ASTORA is confident they are mitigating risks and preparing doctors who treat women living with fecal incontinence with the critical tools and support that they need.

I would now like to invite Dr. Fenner to close our presentation.

DR. FENNER: TOPAS demonstrates a favorable benefit-risk profile for women living with fecal incontinence. With its unique anatomical placement, TOPAS offers an important

new treatment approach. It is minimally invasive, low maintenance, and was proven to be efficacious, safe, and improved patients' lives.

Recall that no single surgical treatment will work for all patients with fecal incontinence. While neuromodulators and anal bulking agents have given us new therapeutic options, a significant unmet need persists. The TOPAS system is the first device providing anatomical support to the anorectum and could reduce the unmet medical need for an effective treatment for fecal incontinence.

Looking again at the TOPAS study, I'll start with a brief reflection on some of the study's limitations that are similar to those we have seen in other recent device clinical trials for FDA using a single-arm design with patients as their own control. While similar to the known epidemiological data on accidental bowel leakage, our population was primarily limited to Caucasian women over the age of 30. Also, the study was not powered to evaluate predictors of efficacy, and we did not identify any one factor that was more likely to indicate success than another. In addition, patients were free to alter their medications and diet that may impact their FI. Finally, while the mechanism of action of this device is not well understood, the study provides evidence that it works.

Turning now to the study strengths, we had surgeons from two disciplines who were able to be trained to safely perform the procedure. We also had over 500 patient-years of follow-up. In addition, many of the objective and subjective endpoints were similar to those used in comparable FDA device trials on FI. Lastly, the majority of the patient-reported outcome questionnaires were validated for use in patients with FI.

The TOPAS study met its primary efficacy endpoint. Overall, 69% of the patients

experienced at least a 50% reduction in the number of FI episodes. The secondary efficacy objectives demonstrated improvements in FI symptom severity and quality of life. Women required fewer visits to their physician and less time off work. They used fewer pads and were less embarrassed.

TOPAS offers patients a safe and manageable treatment option. The pain events were generally mild and, more often than not, required either no intervention or nonsurgical interventions. In the cases of prolapse, which is a common comorbidity in patients with FI, there were no associated adverse events of increased fecal retention or straining. In addition, the position of TOPAS still allows physicians to provide standard of care treatment.

In general, infections were treatable and occurred within the first 30 days. None required surgical intervention, and all resolved in an average of less than 3 weeks. There were eight treatment-related serious adverse events, four of which were due to preexisting conditions and all but one resolved without reported sequelae.

To date, the study has not observed any cases of mesh erosions, extrusions, perforations of organs, dyspareunia, or foreign body reactions. Additionally, there have been no surgical revisions.

It is important to put these risks in perspective. Almost 70% of patients achieved at least a 50% reduction in their FI episodes. Patients who experienced any level of decrease in FI episodes reported improvements in their quality of life. TOPAS is well tolerated and offers patients a safe treatment option. As a physician, I'm encouraged by these benefits and believe that the risks are manageable.

Recalling one of my patients who received the TOPAS device, the benefits were clear. Not unlike other patients with fecal incontinence, this woman had extreme fear about having an accident in public. She limited many of her activities, including flying on an airplane. With TOPAS, she's not only taken several flights to visit family, she has also reported increased confidence and improved quality of life. For her, TOPAS has proven to be a viable option that is both safe and effective.

Beyond one story, it is the safety and efficacy data shown in this clinical study that convinces me that TOPAS should be an option for many of my patients and other women suffering with fecal incontinence.

Thank you. This concludes our core presentation.

DR. TALAMINI: Thank you very much.

We now have a period of about 30 minutes for the Panel to ask clarifying questions. I would remind you, please, to raise your hand to be recognized, push the red button on your microphone when you're speaking, clearly give your name before asking a question, for our transcribers, and then push the button off when you're done.

Dr. Faulx, it would be easy to forget you on the phone, so I will ask you first if you have a clarifying question.

DR. FAULX: No. Can you hear me?

DR. TALAMINI: Was that a no or a yes?

DR. FAULX: No, I don't.

DR. TALAMINI: Oh, yes, we can. Just barely.

DR. FAULX: No, I don't have a question at the moment.

DR. TALAMINI: Okay, thank you.

DR. FAULX: Okay.

DR. TALAMINI: Other Panel members with questions?

Yes, Dr. Afifi.

DR. AFIFI: Abdelmonem Afifi.

I have a question on Slide No. 42. It showed that the percent of African Americans was 7%. Could you tell us why that was not comparable to the U.S. percentage of about 12, 13%?

MR. BELOW: Yes. Paul Below.

I'd like to invite Dr. Fenner to the lectern to address your question.

DR. AFIFI: Okay.

DR. FENNER: Thank you. So pelvic floor disorders certainly have different prevalences in different ethnic backgrounds, and African-American women seem to be protected from many pelvic floor disorders. The pathophysiology or physiology behind that is not necessarily known. So we had made every attempt to try and have a broader representation in our race in the study. However, this is pretty consistent with the numbers of women who seek treatment for fecal incontinence. So we would not have probably expected 7% to 8%, in terms of that ballpark, for African-American women.

DR. AFIFI: And a related question. Did you also monitor ethnicity? Because the question then I have would be what percent were Latinos in the sample?

MR. BELOW: If we could go back and show the demographic slide again. There were nine total patients in the study who were Latino that are represented by the "Other"

category, which was 3% of the study population.

DR. AFIFI: Okay. And my last question is a statistical one on Slide No. 44. The hypothesis, the primary hypothesis is one-sided. You said you were testing whether there was more than 50% who achieved the success definition. So was the test -- were these p-values one-sided or two-sided?

MR. BELOW: These p-values were one-sided.

DR. AFIFI: Um-hum. Okay, thank you very much. Abdelmonem Afifi. These were my questions.

DR. TALAMINI: Thank you, sir. Other questions?

Dr. Iglesia.

DR. IGLESIA: Cheryl Iglesia.

I have two questions as well, about the initial study. So this is a pre-refractory group of women who had 18 episodes, so that's one or two fecal incontinence episodes every day for 2 weeks. So you went from 18 to 5. You're going to down from one or two a day to one every 2 or 3 days. It seems pretty significant. But when I look at your Stage I and Stage II outcomes, looking at the 50% improvement, there seems to be some type of learning curve here because it's 80 patients and 72 patients and you went from 65 to 74, which seems significant to some degree. So I want to comment on that learning curve, particularly since, on your postmarket, you're looking at proctoring just two cases.

And then, secondly -- so that gives you an overall 69% improvement. And then I'm concerned about the 31% of non-responders, and while your logistic regression analysis didn't show predictors, I think I read that several patients had to have some imaging studies

in a subset, and I know that some of the centers, Michigan and Oklahoma in particular, have access to MRIs and ultrasounds that are really on the cutting edge of imaging where mesh is and also baseline defects on pelvical muscles.

So if this sling is designed to replace the puborectalis, I'm just wondering, can we look at even refining it even more and which patients maybe this wouldn't be good for? You know, maybe they already had some tears in the puborectalis that's too far gone. There seems to be a trend in severity of fecal incontinence on your forest plot, although it probably didn't reach statistical significance. There also seemed to be a trend to reach statistical significance between colorectal and urogynecology surgeons.

MR. BELOW: Um-hum.

DR. IGLESIA: So that's lots of little tidbits.

MR. BELOW: Okay. So to make sure that I understand your two questions, you asked about the learning curve and the impact on efficacy results, and then also on potential additional imaging that could be done?

DR. IGLESIA: Well, I'm mostly interested in the non-responders --

MR. BELOW: The non-responders.

DR. IGLESIA: -- and what can you do to kind of -- to basically refine who maybe this isn't a good option for, you know?

MR. BELOW: Okay, thank you. I'd like to invite Dr. Fenner to address both questions.

DR. FENNER: So this is a slide looking at implant sequence, and you see the one to two, then the third and the fourth, et cetera, going up to 10-plus. And so you do see a

slight -- from first 65% up to 73%. This was not -- you know, you see the overlap there of the bars. So it was not statistically significant, but that's why in terms of postmarketing and in terms of the observing, two cases is correct, the idea that physician/surgeons would need to be doing eight a year to continue their certification, if you will, or at least to be offered a rebound. So, as surgeons, we know there is always a learning curve. Where that break point is, we feel like somewhere around eight procedures would make sense. So, statistically it did not show that between the first few or the last.

In terms of non-responders, yes, we're very interested in that group. We were not powered to look at variables. You know, patients had some defecography as well as manometry beforehand, and none of the variables that we looked at could predict success. But you're correct in terms of looking at further evaluations, looking pre and post at the angles of both movement of the pelvic floor, the function with changes in pressures, sensation perhaps. So that will be evaluated.

DR. TALAMINI: Let me just pause the questions for a second to welcome Dr. Thomas Inge, who I think was also a victim of the weather.

Would you like to introduce yourself, your specialty, and your location, sir?

DR. INGE: Sure. I actually don't know. Delta canceled the flight, and it's not quite clear if it's weather, but I appreciate your acceptance of me. I am a pediatric surgeon in Cincinnati Children's Hospital and a surgical researcher and -- yeah, thank you.

DR. TALAMINI: Other questions for the Sponsors?

Dr. Kalota.

DR. KALOTA: Hello. I also have -- Susan Kalota. I also have two questions. It

seemed to me that the infection rate was a bit high, especially with the two abscesses. But how does that compare to other anorectal surgeries?

MR. BELOW: I'd like to invite Dr. Nihira to discuss this question.

DR. NIHIRA: I agree with you, infection is a serious concern. We don't have great data in general about our other procedures. If you look at probably what is the most standard procedure that people do, which is sphincteroplasty, we generally quote about a one in three risk of wound breakdown, which is quite significant. In this case it's important to point out that our infections were quite liberal in terms of how we described them. So it included any investigator impression of redness and that was treated with antibiotic. So these patients didn't get wound cultures. They didn't get blood, you know, looking at an elevated white count, for example.

In specific, you asked about the abscesses, which I think is an important aspect. One of them, in looking at the data, seemed to be more of a seroma that resolved spontaneously, and the other one was treated with antibiotics and seemed pretty mild as well. But we were very conscientious with the concern, especially when it was a permanent implant.

DR. KALOTA: Okay. My other question has to do with the de novo incontinence and prolapse. The incontinence doesn't seem logically associated with the procedure to me. I'd like your explanation of that and also go into the prolapse.

MR. BELOW: Certainly. So I'd like to invite Dr. Nihira back to the lectern to address both of those.

DR. NIHIRA: So thank you for those questions. To go about the urinary incontinence

cases, I think, probably just as an understanding of what we were working with, 46% of our patient population had had prior surgery. Many of them had had slings before in the past. I think it's important to keep in mind that certainly urinary and fecal incontinence or dual incontinence is quite common. So it didn't particularly surprise me with this rate, and I think it had more to do with our observation period.

The next thing you asked was a question about prolapse and -- oh, go ahead.

DR. KALOTA: So do you feel that the incontinence was related to the device?

DR. NIHIRA: No, I do not feel it was related to the device. In terms of the prolapse, this is an image showing what we saw. In particular, you can see that our most common types of prolapse were actually recurrent prolapse. These again, fecal incontinence and prolapse, are both very common comorbidities that women experienced, and many of our women had had prior surgical treatment for prolapse in the past.

The other thing to know is, is that we were incredibly liberal about our inclusion criteria, and women could have vaginal prolapse up to 1 cm beyond the hymenal ring and still be included in the trial, as long as it was not particularly bothersome. So I think given those realities, it wasn't surprising to me to see that rate of prolapse, and I don't think that it was directly related to the implant itself.

DR. TALAMINI: Yes, ma'am.

MS. BERNEY: My name is Barbara Berney.

This may seem like an odd question, but regarding the severity of pelvic pain measurement, were those measurements made while people were using pain relief or without pain relief? Because that does make a difference.

MR. BELOW: I'd like to invite Dr. Nihira to address this.

DR. NIHIRA: So concern for pelvic pain is a huge concern, given this is a new implant. Important to keep in mind that it was standard of care. So we can assume that these patients were receiving pain relievers. In terms of looking at the medications that people received with and without adverse events, at least the numbers of medications looked pretty normal. It's important also to keep in mind that we were using global pain scales out to 1 year. So in terms of precision and in terms of was this the actual device itself, we can just compare our baseline scores to the scores that were last recorded at 1 year, and you can see that they were all -- this is giving you an idea about how much magnitude of pain people had on a global pain score, and then the difference with people's pain was fairly small at the last observation point.

DR. TALAMINI: Dr. Connor.

DR. CONNOR: Jason Connor.

I have a couple questions about pain. So could we see Slide 48? Which is not a pain slide. So I was wondering if we could see something like this. This is for response rate, but a similar slide for pain, a slide that showed perhaps pain by site. So that would be analogous to like Figure 6 in your Panel pack, which showed site by response rate, but for site by pain. Maybe colorectal surgeon versus urogynecologic surgeon broken out by pain as an outcome and then procedure by pain. You talked about learning curve, but it would be interesting to see, I think. So it's kind of those four things. Pain may seem like a bigger issue than efficacy, but broken down by those four items.

MR. BELOW: I just want to make sure that I understand your request to look at the

number of pelvic area pain events between the centers, between the medical specialties. Okay. And then can you -- so I know you want those two.

DR. CONNOR: Right. So by site or surgeon.

MR. BELOW: Okay.

DR. CONNOR: By specialty analogous to this, which is by based upon different demographics, and then the last one was by maybe procedure number --

MR. BELOW: Okay.

DR. CONNOR: -- or how many procedures people have done.

MR. BELOW: Okay. Well, we have done some of these analyses, which I can share. If we could go back. So between the medical specialties, we did look at the pelvic area pain rates, and we saw that the colorectal surgeons had an overall rate of any treatment in the way of pelvic area of pain, 45% versus the urogynecologists. The pain rates by the centers, we don't have that data to display right now, but that's certainly something that we can do and provide for you after the break. The rates of pelvic area pain by implanter experience or implant sequence we also don't have available to present right now, but that's something that we can also provide after the break.

We did do additional analyses similar to our treatment response logistic regression, where we put a number of patient characteristics into a logistic regression model to see if it predicted pelvic pain. I don't have the forest plots to show you, but these are some of the variables that we did use, and the only thing that turned out to be statistically significant was medical specialty. But if you'd like to see the exact forest plots, that's something that we could provide.

DR. CONNOR: Yeah, that'd be great.

MR. BELOW: That would be good? Okay. So to clarify, then, for the things that we will bring and show you after the break, the rates of pelvic area pain by study center, by implant sequence, and then the forest plots that we did in this logistic regression.

DR. CONNOR: Okay. And I was just curious. Is there just one surgeon per site, or did some sites have multiple?

MR. BELOW: Some sites had multiple surgeons.

DR. CONNOR: Okay, thanks.

DR. TALAMINI: Dr. Hicks.

DR. HICKS: Terry Hicks.

A couple of questions. One, in the baseline medical history characteristics for all of these patients, I believe a third of them had depressive disorder, and a third had pelvic pain, and a third had systemic pain. Did you correlate that up to see if there was an effect there?

MR. BELOW: We did include depressive disorders as one of the baseline covariates in our logistic regression for pelvic pain, and that was one of the variables that didn't show a statistical difference.

DR. HICKS: Okay. Second question, a technical question. With the implanting, when you're doing the tunneling, how did you confirm the consistency of how cephalad the sling was placed across the board? You know, because you could just kind make a smaller tunnel. I mean, it's aggressive to get under the mechanism and leave it a little more distal versus more cephalad. So did somebody observe all of the procedures, or did you x-ray

later to find out where the sling actually was, how cephalad it was?

MR. BELOW: I'd like to invite Dr. Nihira to address your question.

DR. NIHIRA: So terrific, we have Slide No. IP-24. So we had a very rigorous standardized training approach. And so this gives the dimensions of where we were making our incisions, 2 cm lateral and 3 cm inferior to the anus. And in order to bring the trocar down to that area, past, around, lateral to the vagina and past that, you had to take a very acute angle, and that essentially had our trainers and our trainees doing that very reliably. In response to your question -- because you couldn't really take a much longer angle. That's why, because the trocar had a finite link to it.

In response to the question of after imaging, we don't have a great way to image mesh currently. Experimentally, people are trying ultrasound, but we don't have like MRI or any coaxial imaging that's useful for that.

DR. HICKS: Okay. What I was asking again is making the tunnel. Okay. People are different, you know, makeup physically, and I think you said you try to put it 2 cm deep to the skin. If you get a really thin person, it's a lot easier to tunnel, and you may end up with a different placing than you do with somebody who's obese, is what I'm getting at.

DR. NIHIRA: Do you mean the post-anal tunnel?

DR. HICKS: Yes.

DR. NIHIRA: I'm sorry, I was thinking that you meant the --

DR. HICKS: No, the post-anal tunnel.

DR. NIHIRA: -- passage of the trocar.

DR. HICKS: Because that's where you're going --

DR. NIHIRA: Correct.

DR. HICKS: -- cephalad to see how far.

DR. NIHIRA: And I would agree, with heavier people it was more difficult. We would actually try to separate their buttocks to minimize that distance that you refer to and try to make it more reliable. Our main goal was to try to be about 2 cm deep.

DR. TALAMINI: Dr. Inge.

DR. INGE: Hi. I was certainly impressed with the efficacy results and the fact that it is a very difficult-to-treat patient population. The focus of my questions will then be on the downside. The pain certainly is, as has been mentioned, an important one. In surgery, we certainly do know that technique matters a lot. And was there any way to record and to begin to sort out whether there was, you know, subtle things that were going on that might distinguish -- you know, might distinguish a group that is having more pain than less? Certainly it's been done in other laparoscopic specialties, and correlations with blinded experts can really pick up things that relate to complications down the road.

Secondly, was there any thought in terms of detecting erosions that, you know, weren't observed? Any thought of anoscopy or any other more precise or more informative measure than perhaps just digital rectal exam?

MR. BELOW: So for the first part of your question, and this is somewhat of a continuation of what we were discussing with Dr. Connor, we did do a logistic regression to look to see if there was anything patient characteristic-wise that predicted who might have a pelvic area adverse event, the 43 patients that had those events. So we were limited kind of in the power of that analysis, but we did include a number of patient characteristics to

attempt to see if there was anything that would be predictive, including whether they had baseline pain, depressive disorders, as we've discussed. We were not able to detect anything in particular that was predictive. However, we recognize the importance of this, and this is certainly something that will be the focus of our post-approval study.

Now, to your point about additional imaging techniques that might have been used for mesh erosion, I'd like to invite Dr. Nihira to the lectern to address this.

DR. NIHIRA: So in my experience -- and sadly, I take out a lot of mesh -- digital exam and palpation seems to be one of the most sensitive ways to detect mesh exposure. And certainly there were centers that were doing anoscopy. That was part of the inclusion, although we did not have a systematic way of doing anoscopy following implantation.

DR. TALAMINI: Dr. Efron.

DR. EFRON: Jonathan Efron.

I have essentially two questions. One is it seems to me that looking at the technique itself, that the degree of tension is a very variable sort of part of the technique that may impact both pain and efficacy, and whether there are specifics on how much tension to place when cinching up the mesh, and whether you found whether that increases pain if it's too tight or decreases efficacy if it's too loose and how you standardize that. That's my first question.

The second question is related to mesh removal. We didn't see any mesh removals with this, but have you had any experience with having to remove the mesh? And how difficult is that when it does need to come out?

MR. BELOW: So I will begin with the instructions that the implanters had for the

mesh tensioning. This is what was provided on instructions for use. They were instructed to conduct rectal palpation during tensioning so that a slight ridge or bump could be felt. I will invite Dr. Nihira to follow up on that and also to address your question about mesh removal.

DR. NIHIRA: So, as a surgical educator, I was really pleased that we had an innovative and standardized way of training tensioning, which we don't currently have for stress incontinence of urine. And what you can see in the model and our three slides is depicting the models that were used both with training and pre-implant rehearsal just prior to implantation. And so what you can see is a simulated anus with two arms, and you can see, in Picture No. 2, when we elevate the arms, the person who had the finger in the anus could feel how much tension. So at our operator training or surgeon training, we all consistently did this and reliably were able to apply a standard amount of tension to create a standard amount of elevation. And this is what we then took back to our respective institutions and rehearsed prior to implantation.

DR. TALAMINI: Dr. Afifi, I think you had a follow-up question.

DR. AFIFI: Yes. Abdelmonem Afifi.

My follow-up question is about the race and ethnicity situation. Because we have such small numbers, particularly of Latinos, probably any tests of the effect of ethnicity or race on outcome would come out to be not significant. Have you looked qualitatively at whether there's anything that would put the question of generalization to African Americans and to Latinos and whether there's any reason to think that the results are or are not generalizable to those subpopulations?

MR. BELOW: Yes, I'd like to invite Dr. Fenner to address this question.

DR. FENNER: So while the prevalence of FI may vary between different ethnic groups, we have no reason to think, for those women, regardless of their ethnic background, that there would be any difference in their etiology per se, at least for FI, and that there shouldn't be any racial differences in anatomic position or the efficacy or response rate to this procedure. So, as I said, we tried to have diverse populations, but again our numbers are pretty consistent with women who seek care for this. But, again, no anatomical reason or pathophysiological reason to think that TOPAS would have any less efficacy in an African-American woman or a Hispanic woman compared to a Caucasian.

DR. AFIFI: What about the more subjective measures of satisfaction or quality of life and so on? We know that those cultural aspects could affect that response.

DR. FENNER: Correct. Well, if we look at FI in other populations, what little data we have to show is that their quality of life measures pretty much correlate with severity across different racial groups. There's not been a significant amount of work in Hispanic women, but in African-American women compared to Caucasian women, when they have the condition and you control for all of the other factors in terms of education or socioeconomic variables, et cetera, that their level of bother would be very similar based on the severity of the condition.

DR. AFIFI: Okay, thank you.

DR. TALAMINI: Dr. Fennal.

DR. FENNAL: Mildred Fennal.

I have a question for clarity on qualifications for this procedure. It says that you

must be 18 years or older in order to qualify for this procedure. But yet, in some of the other writings, it says that you cannot be planning a future pregnancy. And I'm wondering, does that mean at all, no pregnancy in the future? Because if we're bringing the age down, we have to worry about these women in childbearing age, and I saw that you had a 32-year-old person in your study. How did that person make the decision that there would be no future pregnancies? I do think that we have to perhaps consider the childbearing age range when we're talking about a permanent procedure, that you will have no future pregnancies.

MR. BELOW: Yes, thank you. I'd like to invite Dr. Fenner to the podium to address this.

DR. FENNER: So that's a very important consideration. So for the study, it was just, I might say, much cleaner not to have women who were pregnant or certainly desiring pregnancy. You wouldn't want to do it on a pregnant woman just for technical reasons and for blood loss. But in terms of future pregnancies, so I care for lots of women who have fecal incontinence following a complicated vaginal delivery, and those women, as we're taking care of them with TOPAS, hopefully we can help them and correct their problem. If they're going to have a future pregnancy, I would universally recommend a cesarean section so that they do not have another tear or deinnervation injury to the pelvic floor. So I think that it would be perfectly physiologically possible, first, to get pregnant with having a TOPAS in place. And I think that having a cesarean delivery with the TOPAS in place should not at all impact that delivery or the ability to carry a pregnancy. In fact, my opinion is it would be fine to actually have a vaginal delivery with it in place. I don't know that it would, position-wise, impact a vaginal delivery, but my recommendation would be a C-section just

because I would want to hopefully maintain her fecal continence after that delivery.

DR. TALAMINI: Yes, Dr. Fennal, a follow-up?

DR. FENNAL: I think that it would be very important, in the literature that you write, to say how you qualify for this procedure. If it just doesn't say no future pregnancies, that would deter some women who want to have children from having the procedure.

MR. BELOW: Thank you. We'll certainly take that under consideration.

DR. TALAMINI: Yes, Dr. Iglesia.

DR. IGLESIA: So I have a question for you, Mr. Below. And I really appreciate the fact that we're going -- you're going to do an extension to 5 years for safety. But I was just wondering if any consideration was given to potentially using the already built-in Pelvic Floor Disorders Registry, not only for postmarket surveillance but also potentially for a comparison study because this is a single arm. And Dr. Nihira, in his introduction, mentioned other options, including newer fecal incontinence pessaries and/or the nonsurgical neuromodulation efforts. So I was just wondering about that.

MR. BELOW: Yes. I'd like to invite Mr. Rasmussen to the lectern to address your question.

MR. RASMUSSEN: Thank you. Tom Rasmussen.

We have discussed that, and we've had thoughts about how that would happen. And you may know that that registry is currently ongoing with pelvic organ prolapse and the desire of the AUGS society is to eventually have urinary incontinence procedures, and we're not there yet. So I think we're looking at it from a timing standpoint. Certainly we'd like to get our post-approval study going as soon as possible. And, you know, currently, internally

we could get that going a lot faster, build the database and so forth. Not to say we wouldn't consider the PFDR at some point in time. I just think it might take a lot longer to get that up and running, just knowing where that registry is today.

DR. TALAMINI: Dr. Kalota.

DR. KALOTA: I have two questions. One is on the slide with the pelvic pain, it seemed like most of it was mild pain, but were there any patients with significant pain as has been seen in the vaginal prolapse repairs? And the second was addressing Dr. Efron's question on mesh removal.

MR. BELOW: Yes, yes. So we will make sure that we address Dr. Efron's previous question, and then the cases of pain that had significant severity. For both, I will have Dr. Nihira address those.

DR. NIHIRA: And thank you for reminding me. I'm sorry, I missed that one. In terms of mesh removal, there have been no revisions to this device. So what we would be talking about or what I would be talking about would be trying to extrapolate from my experience removing other forms of meshes, and I think the first issue would be the indication of why we were removing the material. Was there a particular circumstance you were wondering about?

DR. KALOTA: The ability to remove the mesh.

DR. NIHIRA: Sure. So, as all other meshes in this area, they're designed to be permanent implants. And I guess my question was for obstruction. We would maybe consider an incisional procedure to incise the mesh, but it's not designed to be removed in total.

DR. KALOTA: Well, in my experience, for vaginal mesh, there are certain people who have pain syndromes related to the mesh. That gets better when you remove the mesh. Whether this is a low-grade subclinical infection or a response to the polypropylene, I'm not sure. But there are patients who need the mesh removed, hopefully in its entirety, and it's not related to obstruction.

DR. NIHIRA: So maybe either trying to address the question of exposure or pain, which are related but somewhat different entities, and I would agree with you that certainly people do benefit from removal of mesh. Again, to date, we don't have an experience with that. But I would think that depending upon the indication, certainly for exposures or erosions, that would lead us to identification of the material and trying to remove as much as is feasible from that area. In terms of pain, trying to remove all of the mesh, just as a transobturator sling, it's not entirely feasible. So removal of as much as possible, we would probably work in that area.

The other issue was the question of pain?

DR. KALOTA: Severity of pain.

DR. NIHIRA: Severity of pain.

DR. KALOTA: Yeah.

DR. NIHIRA: Important to keep in mind again, we were using a global pain score as our main measure. And so trying to put together events of pelvic pain and reported pain scores, there is a little discrepancy. There were a handful of patients who had very significant pain in terms of just the numeric value. And this is kind of what we have at the last -- again, at 1 year, this was their highest pain score rated. We tried to correlate this

with a surrogate measure, which is the PFDI-20 scale.

And interestingly, we had patients who reported a globally high pain score yet very little pain in that region of the body. So there is a discrepancy, but there are a handful of patients. Of the patients who had prolonged pain, the nine, we then tried to compare those who continued on study and those who lost and found no particular patterns to try to define what was going on in terms of was there any similarity or dissimilarity between the character or the location of their pain?

DR. TALAMINI: So our time is up for this section. We've got the opportunity to ask the Sponsors more questions during Panel deliberations. But I'd like to take the privilege of the Chair to ask one final question that I just can't resist. What do you think is the explanation in the difference between specialties in placing this mesh?

MR. BELOW: I'd like to invite Dr. Fenner to address this question.

DR. FENNER: Well, I think that maybe there are a couple of reasons. One is that most urogynecologists that participated in the study were very familiar with the placement of mesh for urinary incontinence or pelvic organ prolapse. So the use of the needle passage instrumentation and the placement or the tensioning of a mesh, that there was -- they started at a higher position in terms of the learning curve because they had that experience. While there wasn't statistical differences between the two groups, there was about a 10% difference in efficacy.

In terms of the pain between the two groups, I think that again, we really need to investigate that more and determine is that potentially a placement difference, a tensioning difference, or is it the fact that, again, for people who are more familiar with the

postoperative pain and the use of a mesh for mid-urethral slings, that they were expecting certain pain levels and that the colorectal surgeons really were more concerned, if you will? I'm not saying that shouldn't have been, but they were more attentive to that as a concern without that experience. Those are a few of my hypotheses. However, I have no data to support any of those. But that would be my explanation until we have better and further data to make those explanations.

In terms of some of the urogynecologists in the group who actually have their patients do some pelvic floor rehab, if you will, or stretching and movement of their pelvis in terms of increasing rotation of the hips and doing things that they feel are in preparation for surgery -- and actually, the patients in two of the larger enrollment centers of the urogynecology group, if you took them out, the pain scores were the same between the other urogynecology centers and the colorectal. So the two larger groups actually have their patients do this sort of pelvic floor stretching prior to surgery. As we are seeing in other surgical specialties, you know, rehab before surgery can certainly impact recovery afterwards. So that too, perhaps, may be an explanation.

DR. TALAMINI: Okay, thank you. I want to thank the Sponsors for clear answers.

It's now 10:02. We'll reconvene at 10:15 to stay on schedule. I'll remind the Panel members not to discuss the issues that are at play here during the break.

Thank you.

(Off the record at 10:02 a.m.)

(On the record at 10:16 a.m.)

DR. TALAMINI: All right, it is now 10:16, and I would like to call this meeting back to

order. The FDA will now give their presentation.

I would like to remind public observers again at this meeting that while the meeting is open for public observation, public attendees may not participate except at the specific request of the Panel Chair.

FDA will also have 75 minutes to present. FDA, you may now begin your presentation.

DR. VALDES: Thank you. Good morning. My name is Thelma Valdes, and I am a biomedical engineer in FDA's Center for Devices and Radiological Health and lead reviewer of the PMA that's under consideration today. Before beginning, I would like to thank the Panel for your time and effort to review this information.

Now, let me start FDA's presentation of ASTORA Women's Health PMA application for the TOPAS system for fecal incontinence.

First, I'd like to acknowledge the review team. As you can see, a number of FDA staff have been involved in the review of this PMA application. Today we will be hearing from select members of the review team whose names are in bold. These team members will cover the clinical data, statistics, and post-approval study plan should this device be approved.

My part of FDA's presentation will briefly describe the device and indications for use, key aspects of the regulatory history, and the nonclinical studies. Dr. Golding will then summarize the clinical study. Dr. Li Ming Dong will then review the statistical data for effectiveness. And subsequently Dr. Cynthia Long will summarize the safety data associated with the device. Lastly, Dr. Bayona will present an overview of FDA's post-approval study

plan. Following the FDA presentation, the Panel will have an opportunity to ask questions of the FDA team.

ASTORA Women's Health proposes the following indications for use for the TOPAS system: "The TOPAS Treatment for Fecal Incontinence is intended to treat women with fecal incontinence (also referred to as accidental bowel leakage) who have failed more conservative therapies."

In subsequent slides there will be a description of what the conservative therapies were and how these affected the endpoints of the trial.

As the applicant has previously presented a detailed description of the TOPAS system, I will only briefly highlight its main device components. The TOPAS system is a single-use product consisting of one mesh assembly and insertion sheaths, two locking connectors, and two insertion needles.

Panel members may be aware that mesh is also used in urogynecology and other clinical applications. In 2011 FDA's OB/GYN Devices Panel met to discuss the use of surgical mesh for pelvic organ prolapse, or POP, and stress urinary incontinence. Until recently, surgical mesh used to treat pelvic organ prolapse were considered Class II devices, regulated through the 510(k). These now have been reclassified from Class II to Class III.

The TOPAS device has a different indication for use, and it is being reviewed as a Class III device through the PMA process. Today FDA asks the Panel to focus on the TOPAS device and the data that are available regarding its safety and effectiveness.

Now I will describe the device in more detail. The mesh is a permanent implant consisting of non-bioabsorbable polypropylene. The mesh is 45 cm in length and 1 cm wide.

The center portion of the mesh is elliptical in shape and is 5 cm in length and 2 cm wide. It's important to note that mesh implants facilitate tissue ingrowth, and once this occurs, they can be difficult to remove.

The mesh implant is covered by removable insertion sheaths, where one sheath covers the central portion of the mesh. At each end, the mesh arm is bonded to the insertion sheath. The insertion sheaths are designed to facilitate the implant's passage through the tissue. Markings on the insertion sheaths are designed to assist with centering of the implant during the surgical procedure.

The locking connectors are color coded for directionality (pink and white) and are attached to each insertion sheath. The locking connectors are designed to attach securely to the needle tips during passage of the mesh implant through the tissue and obturator foramen. Once snapped onto the needle tip, the locking connectors cannot be removed. The trimming process removes the insertion sheaths, the excess mesh remaining outside the body, the connectors, and the attached needles.

To facilitate the insertion of the device, the device comes with two disposable insertion needles. The mesh is to be placed using a transobturator surgical approach, similar to the placement of transvaginal mesh, which Dr. Long will review.

Before moving on to the clinical presentation, I briefly want to highlight the following aspects of the regulatory history with this device.

An application was submitted to FDA to conduct a U.S. clinical trial of the TOPAS system. This single-arm study served as the pivotal study to support PMA approval. The study was fully approved by FDA in March of 2010, and the first patient was implanted in

July of 2010. The last patient was implanted in December 2012. There were a total of 152 patients implanted.

The PMA was filed by the applicant (called AMS at the time) in April of 2014. In July of 2014, the applicant was sent a major deficiency letter, to which the applicant responded 1 year later in July of 2015. A major amendment containing updated clinical information was received at FDA in October of 2015. The clinical information in this amendment is the subject of this panel meeting.

This list summarizes the nonclinical studies provided in support of the safety and effectiveness of the TOPAS system. FDA reviewers have found most of the studies to be adequate. However, the sterilization validation and biocompatibility tests have yet to be found adequate by FDA, and they remain under active review and discussion.

This concludes my portion of the presentation. Next, Dr. Martin Golding from FDA will discuss the clinical trial conducted by the applicant.

DR. GOLDING: Okay. Thank you, Dr. Valdes.

Good morning. I am Martin Golding, a gastroenterologist in the Gastroenterology Devices Branch. I will be providing to the Panel an overview of the clinical study supporting the TOPAS system PMA, which is known as the TRANSFORM pivotal study.

As you've been told and as I'm sure you know already, fecal incontinence, or FI, is defined as an involuntary passage of fecal material or the inability to control the discharge of bowel contents. Fecal incontinence can range in severity from occasional unintentional elimination of flatus to the seepage of liquid fecal material or the complete evacuation of bowel contents.

The frequency of fecal incontinence increases with age, from 7% in women younger than 30 years to 22% in older women. Fecal incontinence is most often multifactorial in etiology and may be attributed to sphincter function, rectal sensation, adequate rectal capacity and compliance, colonic transit time, stool consistency, and cognitive and neurologic factors. Anorectal disease, including hemorrhoids, fissures, or fistulae, are also significant risk factors for fecal incontinence.

Fecal incontinence, as we've already heard, has a major impact on social interactions and is associated with shame, embarrassment, and social phobias leading to a significant deterioration in the quality of life. As a result, symptoms are often hidden by patients, resulting in low rates of self-reporting and therapy-seeking behavior.

Injury to the anal sphincter related to obstetric trauma is known to be the most common etiology of fecal incontinence. Fecal incontinence is also related to -- may also be related to a dysfunction of the puborectalis muscle, resulting in a loss of the obtuse anorectal angle. FI is known to be associated with several other medical conditions such as diabetes, multiple sclerosis, stroke, and dementia.

Conservative medical therapy for FI includes the use of anti-diarrhea medications, antispasmodic medications, fiber supplementation, and biofeedback training. Surgical intervention should only be considered for selected patients who have failed conservative measures and biofeedback therapy. Direct sphincter repair has been shown to be best suited for patients with sphincter defects secondary to obstetric trauma or iatrogenic injury. Sphincter repair has been shown to result in up to a 50% to 80% symptom improvement; however, benefit gradually decreases over time, and incontinence typically recurs.

The TRANSFORM study was a multicenter, single-arm, open-label, two-stage adaptive study. The adaptive study design will be discussed later by Dr. Dong. The purpose of the study was to evaluate both the safety and effectiveness of the TOPAS system for women with fecal incontinence who have failed at least two conservative therapies, including dietary modification, pharmacologic intervention, or pelvic floor muscle training.

The primary effectiveness objective was to show that more than 50% of the study subjects would achieve at least a 50% reduction in the number of fecal incontinence episodes collected over a 14-day period at 12 months compared to a baseline diary. This will be referred to as the $Responder_{50}$ rate. This has been the endpoint used for previous FI studies of PMA devices. The effectiveness results will be discussed by our statistician, Dr. Dong.

There were also several secondary endpoints, which included the long-term effectiveness, reduction of incontinent days, reduction of urge fecal incontinent episodes, and the Wexner score. In addition, several quality of life and other bowel and symptom scores were also evaluated. The secondary endpoints will also be discussed by Dr. Dong.

One of the secondary endpoints was the Wexner score, which is a widely used measure in assessing the efficacy primarily of surgical therapies for fecal incontinence. The Wexner score measures the degree and frequency of incontinence as well as its impact on daily life. The Wexner score is scored from a minimum of zero, which indicates complete continence, to 20, which indicates complete incontinence. The Wexner score correlates closely with both the subjective perception of severity of symptoms by patients and with the clinical assessment by investigators. The Wexner score has also been used as an

inclusion criteria for other FI studies. Typically a minimum score of 10 has been required.

To be considered for the study enrollment, subjects were required to have -- this is not correct. Okay. Okay, we go next. To be considered for study -- okay, to be considered for study enrollment, subjects were required to have four or more fecal incontinence episodes during a baseline of 14 days and have failed at least two conservative therapies such as dietary modification, pharmacologic intervention, or pelvic floor training. Any unintentional loss of liquid and/or solid stool was counted as a fecal incontinent episode. Subjects were excluded if there was preexisting Stage III or Stage IV pelvic prolapse, had undergone a hysterectomy, sphincteroplasty, or posterior surgery within 6 months, or had stress urinary incontinence or an anterior repair within 3 months.

The study enrollment for the TRANSFORM study was 207 subjects, of which 152 subjects were implanted with the device. There were 55 subjects that were not implanted. The reasons included 23 subjects that withdrew consent, 14 subjects that did not meet the selection criteria, and 18 subjects that withdrew for other reasons. The other reasons included lost to follow-up, withdrawn by the investigator, Sponsor termination of a study site, adverse events, and moved away from the study site.

As you can see, 145 subjects completed the 12-month visit, 132 completed the 24-month visit, and 115 completed the 36-month visit. I would mention that 17 subjects have not yet reached the 36-month visit time period.

This is not right. Okay. Why is that not up there? Okay, this is not this. This slide does not have the bottom here.

(Pause.)

DR. GOLDING: Okay. The study population for the TRANSFORM study. The patients had a mean age of 60 years, a mean number of vaginal deliveries that was 2.4. The mean number of fecal incontinent episodes for 14 days was 22, with a median of 18 at baseline. Based on the subjects' bowel diaries, the majority of fecal incontinence episodes were then to be small with a mean of 12 and a median of 10. The mean number of incontinent days over 14 days was 10 at baseline, and the mean Wexner score was 14 at baseline.

Okay. The bar graph shows the age distribution of the study subjects from 30 to 80 years of age. Note that a large proportion of the subjects were between 55 and 65 years of age, with 72% of the subjects being 55 or older and 93% being 45 or older.

This is not the right -- I'm sorry. Okay, study population. Go back a slide. Back another. We're good. All right.

The bar graph shows the age distribution of the study subjects from 30 to 80 years of age. Note that a large proportion of the subjects were between 55 and 65 years of age, with 72% of the subjects being 55 or older and 93% being between 45 -- being 45 or older.

Almost one-half of the subjects had a previous hysterectomy or oophorectomy, and almost half had previous pelvic organ prolapse or urinary incontinence surgical repair in the past. Endosonography has improved the understanding of the incidence of post-obstetric sphincter tears that are potentially suitable for repair and those cases resulting from anorectal surgery. Endosonography demonstrated an external anal sphincter defect in 52% of the subjects and an internal anal sphincter defect in 28% of patients. In addition, more than half of the subjects were felt to have obstetric trauma as the etiology of their fecal incontinence.

Okay. Now we got it. Almost half of the subjects had -- okay. Anorectal manometry was performed on 80 subjects prior to the placement of the device but was not repeated on any of the patients following the procedure. There were significant impairments -- okay. There were significant impairments in all four manometric measurements at baseline, as you can see from the slide. In general, however, anorectal manometry results do not correlate with symptom severity and do not help to predict postoperative success of surgical therapy of fecal incontinence.

Medications for fecal incontinence were used in 40% of the subjects at baseline. The most commonly used medications included opioid receptor agents, bulking agents, and anti-cholinergic drugs. At 12 months there was an 8% increase from baseline in the number of fecal incontinence medications used but a 5% decrease in the number of subjects taking medications. There was no statistically significant difference in the use of fecal incontinence medications between the responders and non-responders at 12 months. Therefore, the use of fecal incontinence medications had no effect on the $Responder_{50}$ rate.

Okay, here we go. In summary, fecal incontinence is known to result in a substantial decrease in a person's quality of life. It is clear that symptoms are often hidden by patients and are both underreported and undertreated. Sphincter disruption secondary to obstetric trauma comprises the largest proportion of fecal incontinence causes in women. In the TRANSFORM pivotal study, 152 female subjects were implanted with the device. At baseline, the mean number of fecal incontinence episodes over 14 days was 22, with a median of 18. The $Responder_{50}$ rate, defined as the proportion of study subjects with at least a 50% reduction in the number of fecal incontinence episodes at 12 months compared

to baseline, was the primary effectiveness objective.

I'd now like to introduce Dr. Li Ming Dong, who will provide the effectiveness data from the TRANSFORM pivotal study.

DR. DONG: Thank you Dr. Golding.

My name is Li Ming Dong, and I am a statistical reviewer in the Division of Biostatistics. I will present the statistical design and the effectiveness results of the TRANSFORM study. Specifically, I will briefly describe the statistical design of the study and then summarize the effectiveness results.

The TRANSFORM study was designed as a multicenter, single-arm study to demonstrate the safety and effectiveness of TOPAS system. One interim analysis was planned to allow possible early stopping to claim effectiveness and to allow the option for sample size adjustment. For doing a single-arm study, ASTORA justified that there was no appropriate control treatment available at the time, and FDA concurred. However, there are some issues associated with the single-arm, unblinded studies.

First, regression to the mean may occur when study subjects' condition is relatively extreme. In this pivotal study, many subjects enrolled with high number of incontinence episodes at baseline. For example, half of the subjects had 18 or more episodes of incontinence during a 14-day period. It is possible that these subjects could show some improvement over time without a medical intervention. This makes it difficult to judge how much of the observed improvement is actually due to the effect of the device.

Since neither the subjects nor the investigators were blinded to the treatment being given, there could be reporting or assessment bias, especially with the evaluation of

subjective endpoints, as in this study. Last, the lack of a control arm complicates the assessment of the device effectiveness and safety, since we do not know how a subject's condition could have changed had they not been treated with the device. We need to keep these issues in mind when evaluating this study.

The primary effectiveness endpoint in this study was based on percentage of subjects who are responders, that is, subjects with at least a 50% reduction in the number of fecal incontinence episodes in a 14-day bowel diary at 12 months post-implant compared to baseline. The responder rate is referred to as the $Responder_{50}$ rate. The pre-specified study hypothesis was that the $Responder_{50}$ rate is greater than 50%. The performance goal of 50% was pre-specified in the protocol, and FDA considered it as acceptable. This hypothesis was to be tested using one-sided exact binomial test at 5% significance level.

The interim analysis was planned to be conducted when 80 subjects completed 12-month follow-up. The pre-specified stopping boundary was 0.0087. That is, if the p-value based on the 80 patients implanted in Stage I was below 0.0087, then the trial would be stopped for early success; if the first stage p-value was 0.0087 or higher, the sample size would be adjusted so that it had adequate power. For testing hypothesis, p-values would be calculated using data from Stage I and Stage II separately. The primary analysis would be done based on intention-to-treat population, that is, all implanted subjects. The protocol pre-specified that the missing 12-month data would be handled as non-responder.

The planned sample size was 152 implanted subjects with possibility to increase based on interim analysis. One interim analysis for effectiveness and sample size adjustment was planned when 80 subjects finished the 12 months, as I just mentioned.

Based on the assumption of 61 responder rate, 152 subjects would give approximately 81% power. Final sample size was 152 subjects, with 80 subjects for Stage I and 72 for Stage II.

This table presents the primary outcome of the study. At the interim analysis when 80 patients implanted in Stage I completed 12-month follow-up, 52 of them, or 65%, achieved at least a 50% reduction in fecal incontinence episodes during the 14-day period. The p-value was less than the pre-specified stopping boundary of 0.0087. Therefore, the primary endpoint was met.

However, the study data monitoring committee recommended that the applicant did not stop early and continue to follow all implanted subjects to obtain long-term safety data. At the time, 152 subjects had already been implanted with TOPAS. The Sponsor followed the committee's recommendation. After all 152 implanted subjects completed the 12-month follow-up, 61.9% [sic] of subjects experienced at least a 50% reduction in fecal incontinence episodes compared to baseline. The 95 confidence interval is 61.1% to 76.3%.

This figure shows that at baseline, the median number of fecal incontinence episodes for all implanted subjects was 18. Three months after the implantation, the median number of fecal incontinence episodes dropped to 5, and it remained stable through 12 months. This change was also reflected in the Responder_{50} rate. At 3 months post-implant, 65.8% of subjects had at least a 50% reduction in fecal incontinence episodes, and this percentage remained stable through 12 months.

The primary effectiveness endpoint was analyzed by various baseline factors that may affect the treatment outcome. It should be noted that these subgroup analyses were conducted to gain understanding of the study outcome and should not be viewed -- and it

should be viewed as exploratory.

P-values and confidence intervals presented are not adjusted for multiplicity and are included for informational purposes only. Since the subgroup analyses were not pre-specified, the p-values and the confidence intervals should not be interpreted as indicators of statistical significance. I will present responder rates by two factors: age and the specialty of clinical center.

This table presents responder rate by four age groups. Each group consists of about a quarter of total patients. As noted, the older women responded to TOPAS better than the younger women did. But there's no obvious trend that suggests the four age groups responded differently to the implant.

The influence of medical specialty of the clinical center on subject's response was also examined. Among the 14 clinical centers that implanted the TOPAS, seven were colorectal centers and seven were urogynecology centers. The urogynecology centers had 72.8% responder rate, approximately 10% higher than that of the colorectal centers; however, the difference was not substantial.

Other factors examined included use of fecal incontinence medication, body mass index, smoking, baseline fecal incontinence episode, vaginal deliveries, fecal incontinence etiology, internal and external sphincter defects, and medical history. None of the factors were found to have important impact on the Responder_{50} rate.

Before I move on to secondary endpoint, I'd like to point out that there were 17 patients with indications of treatment failures. These patients either received alternative therapies for fecal incontinence after TOPAS implant or withdrew for reasons related to

treatment failure.

In the analysis of Responder$_{50}$ at 12 months, 24, and 36 months, based on ITT population, they were considered as non-responders. In applicant's analyses labeled as completed cases only, including analysis for Responder$_{50}$ rate from 12 months through 36 months and the questionnaire data, these 17 patients were excluded at visits after their alternative therapy or withdrawal. Since these 17 patients were mostly treatment failures, results based on a subset excluding them likely overestimates the device benefit.

This table shows the time point when the 17 points received alternative therapy. Three subjects received alternative therapies and/or withdrew for reasons to treatment failure prior to 12-month visits. Fourteen subjects did so after their 12-month visits. Among the 17 subjects, 12 of them had received alternative therapies for fecal incontinence. For other five patients, it is unknown whether alternative therapy was sought.

This table shows the type of alternative therapies the 12 subjects received. Seven patients had implanted a sacral nerve stimulator, three received an injectable bulking agent, and one had sphincteroplasty.

Now I will begin to talk about secondary endpoints. Long-term effectiveness was measured by treatment success at 12 months and 36 months. This table presents percentage of subjects with at least a 50% reduction in fecal incontinence at 12 months through 36 months. The results are based on all implanted subjects. Missing bowel diary data were considered as treatment failure, except for the 17 subjects who had not yet completed the 36th visit. They were subtracted from 152 as the denominator. The

responder rate changed from 69.1% at 12 months to 53.3% at 24 months and 57.8% at 36 months, somewhat reduced but maintained over 50% 3 years after the implantation.

The number of fecal incontinence episodes in 14-day period is another secondary endpoint. This box plot shows the distribution of fecal incontinence episodes at each study visit. The middle bar in the box indicates the median number of fecal incontinence episodes, while the dot indicates the mean. The top and the bottom bar of the box represents 75 and 25 percentile, that is, a quarter of subjects were below and a quarter of subjects were above. Reduction in both median and the mean fecal incontinence episodes were observed from 3 months through 36 months post-implant. However, it is noted that more than a quarter of subjects still had more than 10 episodes during 14-day period from 12 months to 36 months post-implant.

Treatment effect was also measured by reduction in incontinence days. At 12 months, 54.6% of 152 implanted subjects experienced at least a 50% reduction in incontinence days from baseline. At 24 months, 46% experienced at least a 50% reduction. At 36 months, 47.4% experienced such reduction. This also suggests that the treatment effect has a slight decrease over time.

Five instruments evaluating severity of fecal incontinence, impact on quality of life, degree of bother and the distress on pelvic floor and the sexual function. It should be noted that the analyses were all based on available data. Patients with missing data or who received alternative therapies for fecal incontinence prior to the study visit were excluded. Therefore, the treatment effect may be overestimated.

This is Wexner score, which ASTORA has already shown. So I'm going to just skip this

one. It's just to show the general trend.

This is the fecal incontinence quality of life, which you already have seen before.

Pelvic Floor Distress Inventory-20 measures the degree and the bother and distress caused by pelvic floor symptoms. The Pelvic Floor Impact Questionnaire-7 is a shortened version of the Pelvic Floor Impact Questionnaire. It is used to assess life impact on women with pelvic floor disorders. High values represents a more negative impact. Neither questionnaire is fecal incontinent specific, and the total score ranges from 0 to 300. For both questionnaires, lower score represents improvement.

This figure shows that the median score on both measurements decreased at 3 months from baseline and were maintained at the improved levels through 36 months. ASTORA shows the subscale CRADI and the CRAIQ. Both are subscales of these two scales, and the trends are similar.

Pelvic Organ Prolapse/Urinary Incontinence Sexual Function Questionnaire is a short form of questionnaire that measures sexual function. The PISQ-12 has been validated for women with urinary incontinence or pelvic organ prolapse. It is not specifically for women with fecal incontinence. This score ranges from 0 to 48, and a higher score indicates better sexual function. This figure presents mean PISQ-12 score by study visits for sexually active women. The mean PISQ score stayed stable from baseline through 36 month, indicating no obvious change in sexual function.

In summary, the primary effectiveness endpoint was met based on the interim analysis of 80 subjects. For the full cohort of 152 subjects, 69% experienced at least a 50% reduction in the number of fecal incontinence episodes from baseline. Long-term

effectiveness data and patient-reported questionnaire data indicate that the TOPAS system may provide treatment benefit.

This concludes my presentation. Next, Dr. Cynthia Long will present safety information of the TRANSFORM study.

DR. LONG: Thank you, Dr. Dong.

Good morning. I'm Dr. Cynthia Long. I am a medical officer in the Gastroenterology Devices Branch in the Office of Device Evaluation. I have reviewed the TOPAS system's premarket application, and I'll present the safety-related data to you today.

All right. Before presenting the safety data for this device, it will be useful to review a few key components of the TOPAS implantation. As was previously seen, the subject is positioned and prepped, bilateral perianal incisions are made, a 2 cm deep post-anal tunnel is created, and then the mesh is positioned within the tunnel. After identifying the median border of the obturator foramen, two additional incisions are made on either medial thigh. These steps are almost all done under direct visualization.

The TOPAS needle trocar is then percutaneously placed through the obturator foramen and out through the buttock incision in the post-anal space. I'll point out that this part of the procedure is performed without direct visualization and therefore requires a good appreciation of the three-dimensional anatomy of the pelvis, as well as a familiarity with the angulation of the trocar itself. The trocar is then guided through digital palpation within the rectum and vagina to avoid the pelvic organs and the obturator neurovascular bundle.

Once the trocar has completed the proper trajectory, the mesh is then connected to

the needle tip, and the entire trocar-mesh assembly is withdrawn through the thigh incision. In the instructions for use, the applicant recommends adjusting the mesh arms by pulling both ends of the mesh upward until a gentle tension from the mesh is palpable through the rectum. The FDA has identified this tensioning as a potential risk for fecal obstruction which might lead to excessive straining and ultimately pelvic floor dysfunction. The expert opinions of the Panel will be sought on this subject.

I should point out at this point that there were four device malfunctions that occurred during the implantation procedure. Two of the malfunctions were described as the mesh giving way during the tensioning process. One such episode resulted in a pelvic pain adverse event which required acupuncture and narcotic medication. The third device malfunction involved defective markings on the outer sheath. And finally the fourth malfunction involved retraction of the mesh sheath which caused the mesh to catch on the tissue.

Now, let me walk you through the TOPAS system's presumed mechanism of action. Although the exact mechanism of action is unknown, the TOPAS mesh is believed to support the puborectalis muscle in maintaining fecal continence. As depicted in the diagram, the anorectal angle of normal subjects is maintained at an approximately 90-degree angle by the puborectalis muscle and the external anal sphincter. This angulation is believed to keep stool in the rectum and maintain continence through a flap valve mechanism.

In fecal incontinence subjects, a weakened puborectalis muscle fails to create the appropriate angle and thus allows stool to move down the rectum involuntarily. ASTORA has provided mean anorectal angles at rest and at evacuation from 26 subjects'

defecographies, which showed no significant difference in those angles. However, there were technical limitations with the performance of those defecographies. Also, there was variability in angle measurement techniques, and there were too few comparison measurements taken at baseline and 6-month post-implantation in the same subjects to accurately assess the changes in angulation.

The Panel will be asked to discuss the possible association of pelvic organ prolapse, or POP, with the changes in the anorectal angle created by this mesh sling procedure.

Now, with that as a backdrop, I'd like to take a look at the safety data. I should note that the TOPAS system safety profile is based on adverse events collected from all 152 implanted subjects followed for a mean period of 40.2 months post-TOPAS treatment. All safety evaluations were descriptive, and no statistical hypothesis testing was planned for any safety endpoints.

Starting with a high-level view of the adverse events collected, we see there was a total of 684 adverse events reported for all 207 enrolled subjects. There was a total of 677 events reported in implanted subjects. Of those, 562 were non-treatment-related adverse events, and included in that group were two deaths due to cancer. There were two unadjudicated events. One was buttock pain and the other was rectal pain, both of which began more than 3 years after implantation and were ongoing at data closure. All remaining adverse events were adjudicated as treatment-related events.

This slide provides a breakdown of all 115 treatment-related adverse events which were reported in 72 subjects. These events were assessed for their device or procedure-relatedness by the independent adverse event adjudication committee. Seventy-five

adverse events were formally judged to be procedure-related, 24 device-related, and 16 were adjudicated as device- and procedure-related. Combining the two latter categories, there were a total of 40 adverse device events. There were four serious adverse events in the device ADE group, and there were four serious adverse events adjudicated as procedure-related. And I'll provide more detail on those serious adverse events in later slides. But first let's take a look at the adverse events by diagnosis category.

So here we have all 115 AEs broken down by diagnosis category. As you can see, there were 50 pelvic area pain AEs in 43 subjects, comprising the largest number of treatment-related AEs in the study. There were 25 infections reported in 22 subjects, 13 pelvic organ prolapse, or POP, events in 9 subjects, 8 urinary problems, 4 defecatory problems, 1 bleeding event, and 14 AEs categorized as "Other."

Looking at those adverse events that were directly related to the mesh device, we see again that pelvic pain was the most frequently reported with 23 events in 21 subjects. POP was the second most commonly reported AE with 10 AEs in seven subjects. And as you can see here, only two of the infections were adjudicated as device related. Finally, at the time of the data closure, 22 of the 115 treatment-related AEs were still unresolved. And we will talk a bit more about these later.

We will ask the Panel to discuss the safety implications of these adverse events, considering the permanent nature of this device.

In the three slides that follow, I'll present the data on the eight serious adverse events reported. But first, here is a definition. As described in this study, an SAE is any undesirable clinical event that resulted in any of the following outcomes:

- Death;
- Life-threatening adverse experience;
- In-patient hospitalization;
- Persistent disability;
- Congenital anomaly; or
- Any important medical event that was thought to jeopardize the health of the subject or require surgical intervention to prevent one of the listed events.

So, using this definition, not all adverse events that resulted in surgical intervention were considered serious adverse events.

Here we have the four serious adverse events which were related to the implantation procedure alone. And here we have the four device-related serious adverse events, three of which were pelvic organ prolapse-related AEs and one was a chronic pelvic pain described as worsening buttock pain. All four events resulted in surgical intervention.

There were a total of nine events in seven subjects that resulted in surgical intervention to address adverse events. That means that in addition to these four SAEs, there were five additional adverse events with surgical interventions that were not considered SAEs. And here are those five additional surgical interventions, four of which were for pelvic prolapse AEs and one for worsening urge incontinence. In reporting the POP AEs for this study, rectal prolapse events are considered POP.

Before going into detail about the specific AEs by category, let's take a look at the unresolved adverse events in this study. At the data cutoff date, there were a total 22 adverse events still unresolved, and they were as follows. There were nine pelvic pain,

seven POP events, three urinary incontinence, two worsening fecal incontinence, and one described as "Other," which was post-traumatic stress disorder.

Now, let's talk a bit about pelvic pain more specifically. Because pain was the most frequent adverse event type, the data monitoring committee requested that all individual pain events in the pelvic region be combined into one aggregated category. The pelvic area pain sites were as follows.

Now, recognizing the higher frequency of pelvic pain reporting and, as you'll see later, the extended duration of the pain, we thought it was important to take a closer look at how the pain was assessed. During the study, attempts were made to quantify pelvic pain using the non-validated Numeric Pelvic Pain Scale, or NPPS, which essentially rates the severity of pelvic pain on a scale from 1 to 10. Although the NPPS ratings reported are consistent with mild pain, we are concerned that pain scores may not accurately reflect the true pelvic pain in these subjects. Please note the following limitations in capturing the severity of the pain, especially chronic pain.

First, per the study protocol, the NPPS questionnaire was administered to subjects at four time points during the first 12-month period only. When the questionnaires were administered, study subjects were instructed to rate the pain they experienced in the 24 hours preceding their visit. And finally the NPPS means were based upon a limited number of implanted subjects because the pain severity analysis was introduced later in the study. Only 103 out of the 152 had NPPS scores collected at baseline and at the 12-month mean scores. They were calculated off of 91 subject pain scores.

We will ask the Panel if the pelvic pain has been adequately characterized and

assessed.

Now I'd like to take a few minutes to walk you through the time of onset and duration of the data reported. I'll remind you again, the pelvic pain as an aggregated category, there were 50 AEs, 68% where the majority pain events began 30 days or less from the time of implantation, and the remaining events were equally divided between 31 to 120 days and over 120 days onset. As you can see, from the range there were adverse events that occurred more than 1,000 days after implantation.

Now, looking at the duration of the pain AEs, we see that the mean duration of pain was about 313 days or 10 months. Twenty-one out of the 50 pain adverse events lasted less than 30 days, but an equal number of adverse events lasted longer than 120 days. Nine of the prolonged pelvic area pain events in nine subjects are still receiving ongoing treatment as of the data cutoff date.

Here's a table of the nine unresolved pain adverse events, almost all of which had a duration which exceeded 1,000 days or about 2.7 years and well beyond the normal healing period. In this table, the brief narratives show a wide range of symptoms which included such complaints as spasmodic abdominal pain, stabbing rectal pain when sitting, and vulva pain. But also note that some symptoms were episodic or intermittent in nature. These pain characteristics could make it difficult to rate the average pain severity.

As previously noted, the majority (64%) of pain events resulted in nonsurgical treatment. Although a classic dogma in surgery is not to operate for pain without an organic etiology, this information here begs the question of what surgical intervention, if any, would provide pain adverse event resolution without incurring significant risk to the

muscles of continence in the perirectal space. We will talk a bit more about the diagnostic evaluation of chronic pelvic pain adverse events in the next slide.

The following assessments were done per protocol. Subjects were administered the Numeric Pelvic Pain Scale questionnaire again at four visits over the course of 12 months. All subjects had a Q-tip palpation at annual follow-up visits to assess for pain, infection, and erosion. Thirdly, study subjects underwent annual digital rectal exams. Because this diagnostic evaluation was added later in the protocol, these exams were only performed at years 4 and 5.

The Panel will be asked to discuss whether the pelvic pain has been adequately characterized and evaluated, and also the Panel will be asked to provide possible etiologies of the pain that might require additional diagnostic evaluation.

I know we touched on this very briefly and I'll go through it again, but to further analyze the pain, a post hoc analysis of several covariates was done to assess their relationship to pelvic pain outcomes. The covariates were as follows in the slide. And although there was no predefined statistical endpoint, there was a statistically significant difference in several pain outcomes between the two implanter medical specialties. For example, 45% of subjects who were implanted by colorectal surgeons experienced treatment-related pelvic pain AEs versus only 17.4 in the urogynecologists' patients. Other pain outcomes that showed a difference were median time to onset of pelvic area pain, median duration of pain, and unresolved pain AEs.

These results, however, are highly dependent upon two high-volume study sites whose surgeons, both urogynecologists, had extensive experience with the transobturator

technique and encouraged subjects to complete a pelvic floor stretching exercise prior to implantation. When excluding those study centers in the post hoc analysis, there was no statistical difference observed across the study nor specialty.

Now, let's focus a bit on pelvic organ prolapse. There were a total of 13 prolapse events reported in nine subjects. Eight were de novo, and as you can see, two rectal prolapses, four cases of rectocele, one cystocele, and enterocele combined. There were several patients who experienced more than one POP adverse event. There were five POP events adjudicated as worsening based upon a subject's preexisting POP. And there were three cases of worsening rectal prolapse, and one each of worsening rectocele and worsening enterocele, again, multiple events occurring in individual subjects.

As you may recall, there were three SAEs secondary to POP adverse events. And of the 13 POP AEs, seven resulted in surgical intervention. Although subjects with more advanced POP were excluded, subjects were not quantitatively measured for POP at baseline and after TOPAS treatment, nor was there a clear definition of pelvic organ prolapse within the study.

So the Panel will be asked to discuss the possible association of pelvic organ prolapse and the use of the TOPAS sling system.

Now, looking at the POP adverse event onset and duration data that was reported, there was a mean of 350 days onset after implantation. In 92% of cases, the time to onset of the POP was after 120 days. In terms of duration of effect, there was a mean duration of 608 days, and 10 of the 13 POP cases had a duration of more than 120 days. Over half of the POP AEs were ongoing at the time of data closure.

Now, to speak a bit about other treatment-related adverse events, looking now at these less frequently reported AEs, we see that there were four treatment-related defecatory problems in four subjects. They included two worsening fecal incontinence episodes and two defecatory dysfunction events which were described as constipation and obstructive symptoms. Of note is the fact that fecal obstructive symptoms were not collected in the bowel diaries. Both defecatory dysfunction cases occurred and resolved within 30 days of implantation, whereas the fecal incontinence events had a later onset and extended past 120 days.

There were eight urinary problems reported in eight implanted subjects. There was one de novo urinary incontinence and three worsening incontinence AEs. The device effects on urinary problems is possibly confounded by the presence of urinary incontinence in 39 study subjects at baseline. The other four urinary problems were comprised of one dysuria and three urinary retention AEs. All four had early onset and early resolution.

Finally, there were 25 treatment-related infections; 9 were incision site infections, 2 were abscesses, and 14 were categorized as "Other."

Looking more closely at the nine incision site infections, we see that all the infections occurred at less than 30 days, with the exception of one which presented at 33 days with purulent discharge from the left buttock. All AEs resolved within 30 days.

There were two abscesses, both of which occurred within 30 days of implantation and resolved within 30 days after antibiotics and one with incision and drainage.

And finally there were 14 infections categorized as "Other," and they were all adjudicated as procedure-related events.

In summary, the safety profile presented today is based on adverse events collected in 152 subjects followed for a mean period of 40.2 months after treatment with the TOPAS system. There were a total of 115 device- and/or procedure-related adverse events reported in almost half of the implanted subjects.

Pelvic area pain was the most frequent adverse event, comprising 43.5% of all treatment-related AEs and was experienced by 28% of all implanted subjects. Nine pelvic pain cases were unresolved at the data cutoff date.

Another clinically significant adverse event category was POP, or pelvic organ prolapse, with 13 adverse events occurring in 9 subjects. Seven POP adverse events resulted in surgical interventions to address the POP. Six POP events that were not treated surgically were ongoing at the data cutoff date.

And finally there were 25 infections in 22 subjects with this permanently implanted device.

Now, I'd like to close with this benefit-risk review. Based on the totality of evidence, we'll need to determine today if the TRANSFORM study has established a reasonable assurance of safety and effectiveness of the TOPAS system.

In reviewing the benefits, we see that the primary efficacy objective was met with 69% of subjects achieving at least a 50% reduction in fecal incontinence episodes at 12 months post-implantation and 53% of subjects with a 50% reduction at 24 months. The mean fecal incontinence episodes decreased from 21.7 to 9.3 at 12 months, and there were various quality of life measures that showed improvement at the 12-month mark.

Although the data suggests effectiveness in the treatment of fecal incontinence,

there are a number of adverse events just presented which must be carefully considered.

We will ask the Panel if the safety profile supports the device's use as a clinically acceptable risk for the population studied and if there is a subject population in whom this risk would be most acceptable.

Thank you for your attention. Now we will have Dr. Manuel Bayona present the post-approval study considerations.

DR. BAYONA: Thank you, Dr. Long.

Good morning. My name is Manuel Bayona. I am the epidemiologist assigned to review this PMA. I am from the Division of Epidemiology in the Office of Surveillance and Biometrics. I will present the post-approval study considerations for the TOPAS system.

We have been interacting with the Sponsor about the post-approval study proposals and have provided them input, which is reflected in these slides.

Before we talk about post-approval studies, we need to clarify a few things. The discussion of a post-approval study prior to FDA determination of device approvability should not be interpreted to mean FDA is suggesting that this device is safe and effective.

The applicant's plan to conduct a post-approval study does not decrease the threshold of evidence required by FDA for device approval.

The device premarket data submitted to the Agency and discussed today must stand on their own in demonstrating a reasonable assurance of safety and effectiveness and an appropriate benefit-risk balance.

This presentation includes a postmarket question, a synthesis of the extended follow-up of premarket cohort post-approval study proposal, a brief description of the new

enrollment post-approval study proposal, and the FDA assessment of both proposals.

Through the review of the premarket data, the FDA review team has identified long-term safety as a potential postmarket concern that may need to be addressed if the device is approved. In response to FDA concern, the applicant is proposing two post-approval studies, a 5-year extended follow-up of the patients enrolled in the premarket study and a new enrollment post-approval study. The following slides provide a brief summary of the postmarket studies as proposed by the applicant.

This table presents an overview of the applicant's proposed extended follow-up of the TRANSFORM premarket study cohort. It is a prospective, multicenter, single-arm, open-label cohort study. The study population is composed by women participating in the TRANSFORM premarket study. The objectives are to demonstrate long-term efficacy as measured by a 50% reduction of fecal incontinence in a 14-day bowel diary and to demonstrate long-term safety as measured by the proportion of patients experiencing at least one device- and/or procedure-related serious adverse event lower than 25%.

The alternative hypothesis is achieved if the upper bound of the one-sided 95% confidence interval for the treatment-related serious adverse event rate at 60 months is lower than 25%. The sample size is calculated based on the assumption of the 25 performance goal derived from the PMA study of Interstim sacral nerve stimulation for fecal incontinence and the 60-month treatment-related serious adverse event of 12% from the TRANSFORM study for TOPAS system. Under this assumption, a sample size of 70 patients completing 60-month data will achieve 85% power. It is projected that at least 94 patients from the current cohort will complete the 60-month visit, resulting in enough power for the

primary hypothesis test.

Descriptive statistics will be used to summarize the long-term treatment efficacy. Hypothesis testing will be performed by examining if the upper bound of one-sided 95% confidence interval for the serious adverse event rate at 60 months is lower than 25%. Extended follow-up visits are scheduled at 24, 36, 48, and 60 months. The last follow-up visit is projected to occur in December 2017.

This table presents an overview of the new enrollment post-approval study proposed by the applicant. It is designed as a single-arm cohort study. The study population is composed of adult women with fecal incontinence who have failed more conservative therapies. The primary objective is to demonstrate that the proportion of patients experiencing at least one device- and/or procedure-related serious adverse event rate is lower than 20% at 36 months postoperatively.

DR. TALAMINI: Sir, I just want to remind you that the warning light is on and we're a little behind time.

DR. BAYONA: Yes. Yes, I'll finish pretty soon.

The alternative hypothesis will be met if the upper bound of one-sided 95% confidence limit is lower than 20% at 36 months. The 20% performance goal at 36 months was calculated using the serious adverse event rate of 13% from the PMA study of Interstim plus a 7% margin.

Assuming treatment-related serious adverse events of 9% at 36 months for patients receiving the TOPAS system, a sample size of 88 patients at 36 months is required to achieve 90% power with a one-sided 5% Type I error rate. A minimum of 114 patients

implanted with the TOPAS system are needed based on an annual 8% dropout rate. Patients will be followed at 14 to 28 days after the device is implanted and then annually through 3 years.

The secondary objectives include to demonstrate a reduction or improvement from baseline in fecal incontinence and urge fecal incontinent episodes, incontinence days, fecal incontinent symptom severity, and fecal incontinent quality of life as well as Pelvic Floor Distress Inventory. Secondary objectives also include to summarize the frequency, severity, and medical intervention of all treatment-related adverse events; to characterize treatment-related pelvic area pain severity and location; to quantify patient surgical satisfaction and to quantify health resource utilization.

Hypothesis testing will be performed by examining if the upper bound of one-sided 95% confidence interval for the serious adverse event rate at 36 months post-procedure is lower than 20%. Descriptive statistics including mean, standard deviation, median, range, and 95% confidence intervals will be used to summarize the secondary endpoints. Repeated measures model or other statistical method will be used to evaluate changes over time in secondary endpoints.

FDA considers that the performance goals of 25% and 20% proportion of patients experiencing at least one treatment-related serious adverse event seem too high for both the extended follow-up post-approval study at 60 months and the new enrollment post-approval study at 36 months, respectively. These goals were based on the performance of a different device, which is a sacral nerve stimulator. It is removable and does not modify the anatomical structure of the pelvic muscles.

The Panel will be asked to discuss the appropriateness of the proposed safety performance goals and whether the nature of the device, the risk-benefit ratio, and the results from the premarket study should be used to establish the performance goals.

And this is the last slide.

- There is limited data collection in the premarket study.
- The anorectal angle changes were evaluated in only 17.1% of the patients.
- There was no information systematically collected on fecal obstructive symptoms.
- No validated questionnaire to evaluate pelvic pain was used.
- No clear definition of pelvic organ prolapse was included.
- Evaluation of pelvic floor dysfunction at baseline and subsequent visits via a POP-Q-like exam are not included in the current proposals and are needed to assess the association between device placement and pelvic organ prolapse.
- A new enrollment post-approval study could include more thorough and frequent evaluation of chronic pain, pelvic floor dysfunction, and pelvic organ prolapse to assess pain severity and device relatedness.

The Panel will be asked the methods and schedules of diagnostic surveillance proposed by the applicant in the new enrollment post-approval study for following patients in relation to pain, pelvic organ prolapse, and other adverse events such as infection, constipation, and urinary dysfunction; and if there are any additional postmarket concerns that may need to be addressed if the device is approved for market distribution.

As always, we welcome any additional thoughts, discussion, or recommendations

that the Panel may consider appropriate for evaluation in the postmarket setting.

This concludes the FDA presentation. We thank you for your attention. And I apologize because we went over time for a minute. Thank you.

DR. TALAMINI: Thank you very much. I want to thank the FDA for their presentation.

So we now have a brief about 15-minute period for clarifying questions. Again, there's a much longer period this afternoon in which the Panel will deliberate. And if you had any doubt as to why you're here today and hadn't read the questions before, you've now heard quite clearly the issues that the Panel is being asked to grapple with this afternoon. But to enable you to do that effectively, if you need clarification on what the FDA has presented over this last hour and 15 minutes, now is the time to ask them those questions.

Dr. Hicks.

DR. HICKS: Yes. In regard to the statistical structure analysis, you know, we covered a lot of ground, Dr. Dong, but is there anything specifically that you find worrisome about the structure of the study or the statistical work that's done?

DR. DONG: Thank you for the question. To answer your question, my answer is no, I do not have a specific concern about the study.

DR. TALAMINI: Dr. Inge.

DR. INGE: I have a question about design that pertains to the PMA but also may have ramifications for the post-approval. Clarify for me what the considerations were with regard to the control group. I certainly get it that you can't have a sham operation. I

certainly get it that it's -- you know, another procedure may not be apparent that could be used as a control procedure. But if 7% to 22% of women have this problem, there are a lot of women that could form the basis of a comparison group that would get us out of sticky situations, like what is the expected rate of POP in this particular patient population? And we don't have that unfortunately.

DR. DONG: I think I will pass the question to the Sponsor. They probably have better answer.

MR. BELOW: Thank you. Paul Below.

I'd like to invite Dr. Fenner to address this question.

DR. TALAMINI: Dr. Fisher, is that okay?

DR. FISHER: Yes, thank you.

DR. FENNER: So I think the question was, would we be able to use another cohort as a control group? I think that --

DR. INGE: Actually a comparison group, a contemporaneous comparison group to get estimates of expected issues.

DR. FENNER: I think we could do that; we could have women who presented with fecal incontinence who met the criteria and didn't want to be implanted that we then could follow along. We could also -- you know, so we could have a group that we looked at their treatment of fecal incontinence in other ways or just the prevalence and the rise and increase and decrease in pelvic organ prolapse without the implantation. So that could be done.

DR. INGE: I guess the overwhelming reason or overarching reason why it wasn't

done, then?

DR. FENNER: I think in the initial study, we really didn't consider that as a part of the study, and it just wasn't a part of our planning. We were looking at safety and efficacy with the implantation.

DR. TALAMINI: So we'll have opportunity during the deliberations to ask specific questions of the Sponsors again. So I want to try and focus on clarification of the FDA's presentation.

Dr. Fisher.

DR. FISHER: Yeah. I would just like to say we may discuss this at lunch and come back with something, because actually when the original study was conducted, there really wasn't a comparator and now there are comparators. So that might be something that we'll take into consideration. So we may discuss it at lunch and come back with something, also, if that's okay.

DR. TALAMINI: Thank you, Dr. Fisher.

Dr. Afifi.

DR. AFIFI: Actually, I had the same question that Dr. Inge asked. But at this point, I'm wondering whether it would be wise or desirable to get such a comparison group for the post-approval study. So that may be something we could talk about in the afternoon, as well.

DR. TALAMINI: Does the FDA have comments or thoughts on that?

DR. GOLDING: We do have some backup material that refers to five other fecal incontinence devices that have been approved or cleared by the FDA, going all the way back

to 2001. So if you were curious as to the response of other devices and the safety of other devices, we have that information available.

DR. AFIFI: No. Actually, I was talking about specifically the point that Dr. Dong made, which is the regression to the mean. And one way to handle that is to look at a comparison group and see whether the improvement in them is what -- how much it is, and compare that to the improvement in the study group. That's what I was talking about.

DR. BAYONA: Yes, if I may. We have already --

DR. TALAMINI: Could you just give your name before --

DR. BAYONA: Oh, yes, I'm sorry. Dr. Manuel Bayona from FDA, Division of Epidemiology.

We have begun discussions with the Sponsor about the possibility of getting comparators, a concurrent comparator, and we decided to wait until approval of the device in order to see if that was feasible and what would be the best way to do it, because right now the other devices are not necessarily similar in every way because the inclusion and exclusion criteria may be different for each one. So we have to really discuss what kind of comparator will be really the one that we need. So we stopped our discussions more than a month ago, but yes, it was already considered and discussed with the Sponsor.

Thank you.

DR. TALAMINI: Dr. Efron.

DR. EFRON: Jonathan Efron.

I was wondering whether the FDA looked specifically at the patients that developed infections and whether those patients correlated with either the nine patients with pelvic

pain that did not resolve or with a higher proportion of patients that developed pelvic pain.

DR. LONG: That's a very good question. At the break, we can take a look at that and see if there was any correlation. But on immediate recollection, I don't believe there was, but we can come back with a more firm response to that question.

DR. TALAMINI: Dr. Iglesia.

DR. IGLESIA: Cheryl Iglesia.

A question for Dr. Long, with regard to the complications. And, you know, in your summary, 20% of the patients had some type of pain. But when I look at it, it seems like about 5% or that nine were totally unresolved. And, you know, that is the most problematic patient, that one and the patient with the rectal prolapse, because I feel like, you know, this baseline pelvic organ prolapse, which increases as women age, that is easier to treat. Incontinence is also easier to treat. But the rectum coming out and the chronic pelvic pain are extremely difficult. And so the question is, did people make this too tight? Did that lead to it?

And, secondly, there seems to be a baseline issue, and we can look at this with other transobturator devices. I'll just come to mind. I'm not even using -- I'm not even talking about vaginal mesh, and I know there's been complications. This is not vaginal mesh. But if you look at the transobturator to the retropubic slings going through that space, the neurological symptoms are always higher. I don't know if it's in relationship to proximity to nerves or going through muscle and if this is a neuromyofascial versus neuropathic issue, but there does seem to be this baseline 5% going through that with putting mesh in with arms.

So I am going to be asking like, you know, if we can just look at some other studies where we have this information. That might be helpful for the Panel to look at that. The TOMUS trial in particular, anyway.

DR. TALAMINI: Comments from the FDA?

DR. LONG: What I'm hearing you say is it might be helpful to compare the pain that was seen in this study with other studies such as the TOMUS trial. We can look into that and get some information, but we don't have it readily available.

DR. TALAMINI: Other clarifying questions from the Panel?

Dr. Kalota.

DR. KALOTA: Susan Kalota.

I would second Dr. Efron's question for the Sponsor, if they could address it after the break, whether any of the patients with the chronic pain were also the ones with infection.

DR. TALAMINI: Any other clarifying questions from the Panel?

(No response.)

DR. TALAMINI: No? Okay. Hearing none, it's now 11:44, and we will take a 1-hour break for lunch. Panel members, please do not discuss the meeting topic during the lunch amongst yourselves or with any member of the audience. We will reconvene at exactly 12:45. I will ask that all Panel members please return on time. Please take any personal belongings with you at this time. The room will be secured by FDA staff during the lunch break. You will not be allowed back into the room until we reconvene.

So with that, we will start our break. Thank you very much.

(Whereupon, at 11:45 a.m., a lunch recess was taken.)

A F T E R N O O N S E S S I O N

(12:46 p.m.)

DR. TALAMINI: All right, folks, it is now 12:46, and I would like to resume this panel meeting. We will now proceed with the Open Public Hearing portion of the meeting. Public attendees are given an opportunity to address the Panel, to present data, information, or views relative to the meeting agenda.

Lieutenant Commander Garcia will now read the Open Public Hearing disclosure process statement.

Lieutenant Commander Garcia.

LCDR GARCIA: Thank you, Dr. Talamini.

Both the Food and Drug Administration and the public believe in a transparent process for information gathering and decision making. To ensure such transparency at the Open Public Hearing session of the Advisory Committee meeting, FDA believes that it is important to understand the context of an individual's presentation. For this reason, FDA encourages you, the Open Public Hearing speaker, at the beginning of your written or oral statement, to advise the Committee of any financial relationship that you may have with any company or group that may be affected by the topic of this meeting. For example, this financial information may include a company's or a group's payment of your travel, lodging, or other expenses in connection with your attendance at the meeting. Likewise, FDA encourages you, at the beginning of your statement, to advise the Committee if you do not have any such financial relationships. If you choose not to address this issue of financial relationships at the beginning of your statement, it will not preclude you from speaking.

Dr. Talamini.

DR. TALAMINI: For the record, we have received 10 requests to speak for today's meeting. Each scheduled speaker will be given 4 minutes to address the Panel, and unfortunately, given the tightness of the day, we're going to have to stick to that. We ask that you speak clearly to allow the transcriptionist to provide an accurate transcription of the proceedings of this meeting. The Panel appreciates that each speaker remains cognizant of their speaking time.

The first speaker is Ms. Missy Lavender, Executive Director and Founder of Women's Health Foundation, Chicago, Illinois.

Ms. Lavender.

MS. LAVENDER: Thank you, sir.

Our travel was compensated to be here by ASTORA Health. My name is Missy Lavender. I'm the Executive Director and Founder of the Women's Health Foundation, which is a national organization. We're patient-centered, and our mission is to improve the pelvic health and wellness of women and girls. We do that by creating evidence-based programs that are in the area of pelvic health, and then they inform our communication platform and the way we speak to women and girls of all ages and life stages. I'm also a pelvic health patient. I have a lovely 17-year-old son, and we like to say babies take souvenirs, and he took his fair share, and it left me very cognizant of the challenges that women have with issues below the belt. Probably the most challenging day that I can remember from my own personal journey as a patient was about 4 years ago, when I was walking my dog, thankfully very close to my home, and I had this uncontrollable, very strong

feeling that I was not going to make it home before I had to take a bowel movement. And, in fact, all I could do was stand there and be very grateful that I had very tight-fitting yoga pants on with ankle cinches and I was close and there was nobody to witness what I was experiencing, which was devastating, to put it mildly. I went home, I took care of myself, and ever since then, I've dealt with this lovely balance between constipation and fecal incontinence.

So when I was asked to come and speak today, it really resonated for me. As the founder of this organization, for the last 12 years we've seen a lot of innovation in our space, but not very much of it in the area of bowel health and fecal incontinence. You've heard a lot of statistics today, and you understand the incidence and prevalence and the numbers very well. From the quality of life perspective, this is one of the most devastating conditions.

So I am very appreciative of the effort that you're doing today. I really appreciate the research and the data. I would definitely encourage continuing trials, seeing more diversity among the study population. With anything that involves mesh, as a mesh patient and a mesh rejection patient, I know that it's a scary word for a lot of people. In this particular case, it gives me encouragement to know the caliber of the healthcare providers who are implanting it. And obviously when it comes to market, I'm hopeful that this team will ensure that it's done by people who are very well trained.

And I thank you for your time.

DR. TALAMINI: Thank you very much.

Our next speaker is Ms. Linda Smith. And, Ms. Smith, if you could give us a little

context, that would be helpful, please.

MS. SMITH: Okay, my name is Linda Smith. I am 65 years old, and I came from Norman, Oklahoma. I would like to say that ASTORA has paid my way here today, but they are not paying for any of my personal time.

I worked at the University of Oklahoma and retired recently after 26 years. I spent most of that time working in development and in the Price College of Business. And as you can imagine the University of Oklahoma, I'm sure you all have heard of the Oklahoma Sooners. And so working with development required me to travel. It required me to go to sporting events and meet with alumni and donors, and sometimes I would have to run out of the room, or I would be sure and wore a coat and drag it around my waist if I had problems before I made it out of the room.

I didn't really have any friends that I could talk to, except I was very lucky to have a gynecologist that I could speak freely to. And after one of my annual exams, she looked at me, and she could tell there was something wrong and she asked. And with tears in my eyes I told her. I told her of the times that I couldn't make it to the bathroom, the times where I brought extra clothes to work, and I didn't know what the problem was. Was it something I was eating? Was it something I was doing or not doing? And she assured me that I was perfectly normal, that it was things that happened to women, and there were ways to fix it, and that's all she had to say.

She transferred me. She referred me to the OU Health Sciences Center, the physician center, and the doctors there started me out, and later Dr. Nihira started the clinical trials. I spoke with him. I gave him my fears and my hopes that what might happen

could make me better, make me feel more comfortable and like a woman again, because this does -- it takes away that feeling of being -- wanting to be intimate, wanting to go out and have fun and just be yourself.

And so I hope today that you will think of all of the women out there, whether they're young, old. I'm 65 years old. Some of these women may have it earlier, some may get it later. But at whatever age, if it works, and this did for me, I hope that you will consider this and think about your wife, your daughters, your mothers, and help us all to feel human again.

Thank you.

DR. TALAMINI: Thank you very much, Ms. Smith.

Next is Ms. Trynisha Cheadle, Research Project Coordinator, University of Oklahoma Health Sciences Center, Oklahoma City, Oklahoma.

MS. CHEADLE: Hello. Thank you for your time. ASTORA Health supported my travel here today. I have no other further financial disclosures.

Again, my name is Trynisha Cheadle, and like you said, I am a research project coordinator as well as a licensed practical nurse clinician with over 11 years of nursing experience and over 6 years of experience in clinical research and more than 4 years of experience serving as the lead research coordinator in the section of urogynecology, again, for the University of Oklahoma Health Sciences Center.

I, along with the other research nurse, personally see the research patients for their clinic appointments and facilitate their care and plan for future appointments, and in doing so, we are able to build strong personal relationships with our patients. Today I come

before you just to express my thoughts about the TOPAS sling system for women and how it is a benefit for patients who suffer with fecal incontinence.

We understand that treating women who suffer from fecal incontinence is not a medical emergency or a matter of life or death. However, it does affect the quality of life our patients are able to live. I have seen patients who are otherwise healthy and able to live an active life, but instead must live a limited life, one that requires staying near a bathroom or not being able to do the simple yet enjoyable things in life, such as going to church, going to a movie, traveling, visiting with friends and family or even just going out to dinner at a restaurant, all because of the embarrassment of having accidental bowel leakage and the fear of others seeing or smelling stool on them.

After treatment with the TOPAS sling, the majority of our patients have reported having a decrease in the number of accidental incontinence episodes to no accidental incontinence episodes at all. Patients have stated that they have their confidence back and are so pleased with the results. They are able to do things they haven't in a very long time, such as leave the house without wearing a pad or taking a change of clothes with them.

In closing, being able to offer the TOPAS sling as a treatment to women who suffer with fecal incontinence is a great option. A few of our patients were asked, knowing what you know now, would you do it all over again? And their answer was yes, because to them the benefits outweigh the risks. They now have control over their bowels. The TOPAS sling has given them quality back into their lives, and I ask that you keep these patients in mind as you consider your decision today.

Thank you.

DR. TALAMINI: Thank you very much.

Next is Dr. Peter L. Rosenblatt, Director of Urogynecology, Boston Urogynecology Associates, Mount Auburn Hospital, Cambridge, Massachusetts.

Dr. Rosenblatt.

DR. ROSENBLATT: I can't speak without slides, you know? Good afternoon. My name is Dr. Peter Rosenblatt, and I'm the Director of Urogynecology and Reconstructive Pelvic Surgery at Mount Auburn Hospital in Cambridge, Massachusetts, and an Assistant Professor of OB/GYN at Harvard Medical School. I'm also the -- it's not going. I'm also the inventor of the TOPAS procedure. Thank you. And this is my disclosure slide, and ASTORA did not compensate me for coming here today.

Fecal incontinence, or FI, is a socially devastating and embarrassing condition for women. Only about one in five women with FI have discussed the problem with any healthcare provider. So it remains a taboo subject, although that seems to be changing in recent years as more treatment options, both conservative and surgical, as we've heard today, become available to physicians and to their patients.

If you could advance it, thanks.

Treatment of FI, though, can be challenging. Until recently, after conservative measures that you've heard about with diet, exercises, and medications, the only viable surgical option we had was anal sphincteroplasty, which is often painful, and it's prone to wound breakdown and infection, and in most surgeons' hands, it only provides limited long-term success. More recently, sacral neuromodulation has become available and is effective, but it has its drawbacks as well. It's expensive and you need to have regular battery

replacements.

In the early 2000s, about 12 or 13 years ago, I made a couple of observations that led me to the development of the TOPAS procedure. First, I noticed that many of my patients with FI were lacking the normal anorectal angle, which is the approximate 90-degree angle between the anus and the rectum and is thought to be an important part of the continence mechanism. It acts like a flap valve, as you've heard, between the rectum and the anus. In many of my patients with FI, when I did a digital exam, my finger would not have that angle. It would go straight back to the coccyx.

And a corollary of that -- and that's due to the weakness of that puborectalis muscle. A corollary of that is that as soon as you do an exam, there would be stool right there at the anal opening instead of higher up where it should be stored in the rectum. And you can only imagine the amount of urgency that a woman must feel when there is stool sitting right at the anal opening.

If you could, thanks.

So my goal in developing the TOPAS procedure was to provide support to the anorectum, to compensate for the loss of pelvic floor muscle function, and to prevent entry at rest of stool getting into the anus.

As you've heard, fecal incontinence is not a condition that is life-threatening, but it really does take away a woman's life. Even if accidents occur infrequently, they're not predictable. So women live in constant fear of worrying that they're going to have an accident at any time. They often limit their social activities. They become depressed and isolated. These women are desperate for a solution for this embarrassing problem.

I've now been performing a TOPAS-like procedure in my practice for over 10 years, and I found it to be safe, reproducible, and effective. It's been extremely gratifying for me to see women returning for postoperative visits who tell me how this procedure has improved their symptoms. It has given them their confidence and their self-esteem back. I recently saw a patient that had TOPAS about a year ago, and after the exam, I was leaving the exam room, and she turned to me and just simply said thank you for giving me my life back. I can tell you, there's nothing more gratifying than hearing that from a patient.

So now that you've heard everything, I hope that you will vote favorably for this.

Thank you.

DR. TALAMINI: Thank you very much.

Next is Ms. Cecile Howard. And, again, Ms. Howard, if you could give context, that would be great. Thanks.

MS. HOWARD: Yes. Hello, my name is Cecile Howard, and I'm 57 years old. I am from Marlow, Oklahoma. ASTORA Health supported my travel here today, but I haven't been paid for my time.

Like I said, I'm 57 years old, and I had fecal incontinence for over 20 years. I traveled here today with my husband to tell you my story because I felt it was important for you to understand why a treatment like TOPAS is important for women who are hiding from their lives because of fecal incontinence.

My condition started with spasmodic colon, irritable bowel syndrome. At first the fecal incontinence was only minimal, but after having irritable bowel syndrome for roughly 5 years, my sphincter started to deteriorate, and the fecal incontinence grew much worse.

By the time I had the TOPAS procedure, the fecal incontinence was severe enough I could be in a room adjacent to the bathroom and still not make it to the bathroom before having an accident. I was so embarrassed from the frequent accidents that I did not want to leave my home. I could not go on family outings without making sure there were restrooms close by.

I worked at LegalShield and had an incident where I was not able to make it to the restroom in time. The restrooms there were in the rear of the building, so I had to walk in front of all of my co-workers in order to go leave. It was so embarrassing that I did not ever want to go back there to work.

My family physician knew of a study for fecal incontinence and referred to me Dr. Nihira at OU Medical to see if I could be a candidate for the procedure. The TOPAS device has been a life-changing miracle for me. I have not had to be concerned with bouts of fecal incontinence since the device was put in. Now I can go on family outings, go to restaurants, go to the movies, and go shopping without having to be restricted by how close a restroom is.

As you think about your decisions today, I ask you to remember my story because it is a story of many other women like me who are struggling with and hiding because of fecal incontinence. They need TOPAS to return their lives to normal.

Thank you.

DR. TALAMINI: Thank you very much.

Next is Ms. Marta Hill Gray, Women's Health Foundation, Chicago, Illinois.

MS. GRAY: Good afternoon. My name is Marta Hill Gray, and ASTORA Health did

pay for my travel expenses, not my time.

My name is Marta Hill Gray. I am a women's health advocate, and I'm here today with the Women's Health Foundation. We are an organization, as Missy Lavender said earlier, dedicated to women's health, women's pelvic health specifically, and I want to speak on behalf of millions of women who suffer with fecal incontinence.

We know too well this is not a condition any woman ever thinks will happen to her. And sadly this is a condition more common than any of us really know. And I'm so moved by what's been said earlier, I'm just going to share that my mother suffered with it for 8 years before she died, and she died recently, and she was completely trapped in her home, and she took medication for her episodes.

But a day after an episode, she was so unsure of herself that she would cancel going anywhere, she was so worried. There weren't enough pads or diapers in the world to give her the confidence that she needed to leave her home, and as a result, she missed graduations, she missed weddings, she missed special occasions that at the end of her life really left her very sorrowful and isolated alone. Her husband didn't want to go without her.

So just that one sliver of sorrow that I have experienced through watching my mother lose a very big part of her life, at the end of her life, to enjoy her grandchildren and those kinds of things. It's a powerful, powerful story, and there are millions of these stories out there. So I just want to make sure to raise my flag for my little mommy, to say that it happens. You know, we're all touched somehow by this, closer than we think.

It bears repeating that nearly 18 million adults in the United States have this. By

2050, 20 million women are expected to have fecal incontinence in the United States due to the aging population.

Another thing I wanted to mention is I've worked in women's health for some time, and as we all know, women are very reluctant to talk about anything pretty much below their belts, whether it's their menstrual cycle, sexual issues, painful intercourse, menopause, birth control, child birth, pelvic floor issues, fertility, bladder leakage. All of these topics women are loath to discuss with their healthcare providers. I promise you, even in the menopause space, they're having a terrible time reaching women to talk about what's happening as their bodies change and they age. So this is just part and parcel of an aspect of women's health where we're not excited to talk about it and we don't know who to talk about it to.

So I really encourage all of us to remember that as these opportunities come forward for women, that we make sure that their healthcare providers are aware of it and that they're aware of it as they go forward.

Also, of course, there are other treatment options. This is not anyone's first choice, to have a surgery to take care of this. But we know the good news is exercise and medications are great alternatives. I support those lines of treatment as the preferred path. However, those that require more dramatic and invasive options need choices that are safe and reliable.

I want to also mention, the TOPAS option we're discussing today is one that is probably not the first choice. Surgery rarely is. Given the women who've had a positive outcome in the trials, I encourage the FDA to continue to keep an open mind and a close

eye on new treatments such as this for women whose lives have been stopped cold by this crippling condition. By having safe and effective treatment options and choices, women can begin to have hope, regain their lives, rather than to have to cope on a daily basis, something that the rest of take for granted.

I strongly suggest you continue to support and guide to market, using the scrutiny and expertise of your trusted advisors, every possible option, including the TOPAS device discussed today, to help improve the lives of the millions of women suffering from this debilitating health problem.

Thank you.

DR. TALAMINI: Thank you very much.

Our next speaker is Ms. Bonnie Allison.

MS. ALLISON: My name is Bonnie Allison, and I'm 73 years old. ASTORA Health supported my travel here today, and I have no other financial disclosures.

I developed fecal incontinence about 10 or 12 years ago. I had been a long-distance cyclist, having been the first official women's finisher over 50 in the bicycle Race Across America, which was 2,909 miles, a record I held for 19 years. I still hold some 12- and 24-hour age group records for bike racing and was all-American dual athlete one year. I was an ultra marathon runner having completed one 100-mile trail run and several 50-mile and 50k runs and still hold a record of running 64 miles in 12 hours. I had been treated for runners diarrhea, which I never had, so the treatments didn't work since I had the problem even when I wasn't running.

And I had gotten so bad I had to run in my neighborhood where I could be within a

mile of my house, and oftentimes I could not even make it back to my house without an accident. I always had extra clothes at work and in my car. I was too embarrassed to tell my running friends what was going on, so most of them did not know when I -- that I had gotten the TOPAS device.

I had been to many doctors, one of which wanted to do a colostomy, and needless to say, I never saw her again. I saw an ad in the newspaper about the study and called one of my doctors and talked with him about it. He was very supportive and advised me to see if I qualified for the study. I called and was accepted into the study.

I had the procedure done almost 4 years ago. I rarely have an accident and no longer have to be afraid to go out in public or go for a long run. This past summer, I completed two half marathons and two 25k runs without any problem, and I no longer have to miss the long runs because of fecal incontinence or the long bike rides.

As you think about your decision today, I would ask you to remember my story and the success I have had. The TOPAS device would benefit many other women like me who were ashamed to let anyone know of their condition.

Thank you for allowing me to tell my story.

DR. TALAMINI: Thank you very much.

The next speaker is Mr. Jay G. Ronquillo, National Center for Health Research, Washington, D.C.

DR. RONQUILLO: Thank you very much for the opportunity to speak today. My name is Dr. Jay Ronquillo, and I am speaking on behalf of the National Center for Health Research. I am a physician who trained at Massachusetts General Hospital. I have two

engineering degrees from Cornell, a master of public health from Harvard, and a master's in biomedical informatics from Harvard Medical School. These are the perspectives I bring with me today.

Our research center analyzes scientific and medical data and provides objective health information to patients, providers, and policymakers. We do not accept funding from the drug or medical device industry, and I have no conflicts of interest.

Fecal incontinence is an important clinical condition affecting the quality of life for many patients for which few effective treatments exist. In order to determine if the product presented today addresses that unmet clinical need, we should consider the risk-benefit profile of this device and put it in the proper context of related products currently being marketed to patients.

DR. TALAMINI: Sir, if I could just interrupt you. If you could get a little closer to the microphone for us, please.

DR. RONQUILLO: Okay.

DR. TALAMINI: Thank you.

DR. RONQUILLO: Is that better? The study provided a detailed description of adverse events, some of which appear to resolve. However, the remaining unresolved adverse events represent an important concern for patients, including chronic pelvic pain and pelvic organ prolapse, which can have serious long-term consequences on quality of life. Given the recent public safety concerns for surgical mesh products used for other indications, better data are needed so patients can understand the full impact of these potential complications.

The TRANSFORM study suggested a reduction in the number of fecal incontinence episodes and incontinence days, along with score improvements in some questionnaires assessing quality of life. However, the single-arm, unblinded study design is inadequate to provide conclusive results. It is not possible to assess the true effectiveness of this device without a control group to provide context for these findings.

Previous studies have shown that control groups, even those with sham surgery, often improve significantly. Would patients in some kind of control group show similar improvements without the device? How would these patients respond to newer conservative therapies that are now on the market? These are important questions that patients, physicians, and the FDA will need to answer in order to evaluate the device's effectiveness.

The proposed indication for the device is for treating women suffering from fecal incontinence who have not responded to more conservative therapies. However, the study targeted a much smaller subpopulation of patients than the proposed indication suggests. For example, some key groups were excluded from the study, that is, women who are pregnant or have a history of pelvic organ prolapse, stress urinary incontinence, or relative rectal or pelvic surgery.

In addition, other important subgroups, such as younger women, made up a relatively small fraction of the study. As a result, the proposed indication, as currently described, includes patients for which there is little or no data supporting safety and effectiveness, such as young and/or pregnant women.

In summary, the lack of a comparison group or data support for substantial groups of

women mostly likely to suffer from fecal incontinence makes it impossible to determine if this device would benefit them. A control group is needed to determine if the device is effective for anyone. And if it is, it should be approved only for the types of women studied, not for the types of women who were intentionally excluded. We encourage you to recommend that these studies be conducted before a decision is made about whether or not to approve this device.

Thank you again for the opportunity to speak today and for consideration of our views.

DR. TALAMINI: Thank you.

Next is Dr. Patrick Culligan, investigator for TRANSFORM trial implants. And if you could also share any additional positions with us, that would be great, Dr. Culligan.

DR. CULLIGAN: Sure. I sure will. My name is Dr. Patrick Culligan, and I am a urogynecologist in northern New Jersey, and I'm also a Professor of Obstetrics and Gynecology with Mount Sinai Medical School in New York. I have been treating patients with, among other things, fecal incontinence for greater than 20 years. And in addition to having a very busy clinical practice, I'm also a very busy clinical researcher with over 65 peer-reviewed publications, and I run a fellowship program. I was, as you said, an investigator in the TOPAS trial, and in fact, my site along with another site were tied for implanting the most TOPAS devices during the surgical trial. I cleared my schedule today to come here and testify because of the experiences that I was able to witness with my patients having this surgery.

And I just want to say that I want to salute the women who came to tell their stories,

because I certainly asked a number of my patients whether they would want to come and do that, and they all said no, even if they were, you know, 100% happy. It can be a very embarrassing thing to talk about. But I can tell you that the experience that these ladies have been describing is the normal experience after the placement of the TOPAS device, not just initially but long term in my experience. Of course, we have patients who do have disappointing results. But even those patients who are more disappointed with the results said they would do it over again. And that's because the TOPAS procedure is -- if any surgery qualifies as a minor procedure, the TOPAS procedure is that.

I did these surgeries all within about a 15-, 20-minute time period under local anesthesia with sedation, and they all went straight to what's called the second stage of, I guess, a launching pad, the last place you go before you leave the hospital right after the operating room, and they were all leaving the hospital within 1 or 2 hours after the procedure. And a woman took very little pain medicine, if any, afterwards. And so if they were even disappointed in the results, which is only a small handful of the patients that I implanted, they would all do it over again because at least they tried.

The final thing I want to mention is my go-to procedure before the TOPAS procedure was available in this trial and I hope will be available in the future. It was an external anal sphincteroplasty. It's a major contrast. If you're going to treat fecal incontinence with an external anal sphincteroplasty, you need to warn the patient that that procedure produces literal agony. It's one of the most morbid procedures you can do for somebody because they can't really treat their pain because, even though it's immense, if they treat the pain with pain medicine, they're going to get constipation, which then results in more pain. So

it's a bad cycle. The external anal sphincteroplasty produces huge morbidity. The TOPAS device produces almost none, and they have about the same efficacy over time.

So, in summary, I'm hoping that I'll get to use this device again as soon as possible.

DR. TALAMINI: Thank you.

And our last scheduled speaker, Mr. Donnie Howard.

MR. HOWARD: Good afternoon. My name is Donnie Howard, and I'm married to Cecile Howard. ASTORA Health supported my travel here today, but I have not been paid for my time.

I cannot speak about how it feels to suffer with fecal incontinence, but I've experienced watching someone who means the world to me suffer with this condition for over 20 long years. I came here today to try to convey what a relief it is to see my wife not have to suffer from fecal incontinence and the embarrassment that accompanies these frequent accidents, all because of the TOPAS procedure.

About 5 years ago, my wife came home from her personal physician, talking about a study for a new procedure to treat fecal incontinence. This study was to be conducted at the OU Women's Pelvic and Bladder Clinic in Oklahoma City by a man named Dr. Nihira. I am real old-fashioned, and I won't be anyone's guinea pig for a test case, and I didn't want her to be either. But after a long conversation with my wife, I agreed to go to Oklahoma City and see what the doctor had to say. Dr. Nihira did not make any wild promises, but he did speak very positively about this procedure helping with her fecal incontinence condition. He did not represent it as a panacea for her problem, but he did say it would give her more control. We discussed the procedure, and after some convincing from my

wife, I agreed to go ahead. I understood her desperation. She was subject to having an accident at any time, anywhere, regardless of diet or activity. Up to this time, nothing we tried helped with her fecal incontinence. There were no post-surgery complications, and her life was immediately changed.

For 20 years she had experienced problems with fecal incontinence, and we altered our activities to accommodate these problems as well as we could. We no longer even consider proximity to restrooms as the number one priority for choosing what we will do. I can't thank Dr. Nihira enough for helping my wife with this amazing TOPAS device procedure. It's more wonderful than you could imagine seeing my wife happy to go and do with the family like normal once again. Please consider her story when you make your decision today.

Thank you for your time.

DR. TALAMINI: Thank you, sir.

So that concludes our scheduled public comments. Does anyone in our audience wish to address the Panel at this time? If so, please come forward to the podium and state your name, affiliation, and indicate any financial interests. You'll be given 3 minutes to address the Panel.

(No response.)

DR. TALAMINI: Seeing no respondents, we'll now pronounce the Open Public Hearing to be officially closed, and we will add -- I'd like to please add the Panel's thanks for commenters, particularly patients, to come forward and share those stories. We're very grateful. Thank you.

We will now continue the Panel deliberations. As a reminder, although this portion is open to public observers, public attendees may not participate except at the specific request of the Panel Chair. Additionally, we request that all persons who are asked to speak identify themselves each time. This helps the transcriptionist identify the speakers.

For the Panel members, I would encourage you at this time to get out your copy of the discussion questions. As we deliberate, we are going to come to a time where we will need to address each of these questions that are in your binder and give the FDA this Panel's opinion on each one of them. So the purpose, the focus, the thing that we're getting to during our upcoming time of deliberation is answering questions and discussing among ourselves, as Panel members, with the help of questions to the Sponsors and the FDA, outstanding issues in your minds, our minds about these questions that we're going to be directly addressing a little bit later on.

Now, this morning there were some issues that we asked the Sponsors to address. Are the Sponsors prepared to respond to those questions posed this morning?

MR. BELOW: Paul Below.

Yes, we are.

DR. TALAMINI: Okay. So if you could please go ahead with that response now. Thank you.

MR. BELOW: Thank you.

So we did do the additional analyses requested. Before we do so, I would like to clarify one point about mesh removal that Dr. Efron and Dr. Kalota brought up, and I'd like to invite Dr. Fenner to the lectern to discuss that, and then we will show the analyses that

were requested.

DR. FENNER: All right, thank you. I am Dr. Dee Fenner from the University of Michigan and one of the site investigators.

So I wanted just to address your question about the removal of the mesh. So the removal of a mesh is a surgery that many of us who take care of women with pelvic floor disorders have become familiar with over the last several years. So I thought a lot about this as I've implanted the TOPAS system and what I would do if I needed to explant the mesh. So I just show here a coronal view of the mesh in situ, and the way I would approach this would be, first, I would try to use the aid of ultrasound, because with some skill at many centers, you do have the availability of a 3D ultrasound that you can facilitate visualization of the mesh and you can do that in the office as well as in the operating room.

I would make -- identify the two post-anal incisions. Having examined many of these women now who are at 3 to 5 years out, I can tell you some of those, they do fade, and it's sometimes hard to even see the incisions. But I think in the operating room we'd be able to see those scars. I would open up post-anally and identify the mesh, and then I would probably transect it in the midline and grasp each end of the sling behind the anorectum.

From there, I would have marked from the scars that are from the placement of the obturator space there. That sort of would probably mark with a pen or with the ultrasound the track of where I anticipated the mesh to be. So that's a guide visually for myself to know where the mesh is. I would inject or infiltrate around the mesh through that post-anal incision with, in my practice, a vasopressin solution to try to help free up the mesh by just squirting some solution around it as well as to help with bleeding. I would use a tonsil

or, for the non-surgeons, just a small instrument to start opening up the perirectal fat and move up and to free that sling as far up as I could, safely go towards the obturator foramen and towards the obturator membrane where the sling is. I would then go from above those obturator incisions and open that up, find that end of the mesh, and with some gentle traction and movement back and forth, I believe that I would be able to explant the mesh on each side.

So while that's in a non-infected mesh situation, for those of you who remove mesh, you know that can be quite difficult and daunting in terms of the ingrowth of tissue and vascularity into the mesh. But, you know, having removed over 100 meshes from other areas in the pelvis over the last several years, I do believe that I safely would be able to explant the sling.

MR. BELOW: To address Dr. Connor's questions about treatment-related pelvic area pain events, including the forest plot with the demographic variables, the rates between the rates at centers, and also the implant sequence, I'd like to invite Dr. Nihira to the lectern.

DR. NIHIRA: So we spent a considerable amount of time trying to see if there was a predictor based on the data that we had of the pain events and reported pain events. We broke it down into whether patient factors, whether they're performer factors or whether they're performance factors that contributed to it.

And in response to the question about patient demographic characteristics, we looked at several different things. They're all represented by age, by health status in terms of severity of incontinence, by having a sphincter defect or not. We have some things like they came close, like the fecal incontinence severity. But when we did an analysis with a

Fisher's exact test on that variable, we weren't able to find any correlation between that kind of a predisposing factor on a patient characteristic and with having the episode or reported adverse event of pain.

In terms of asking the question about medical specialty, we were quite interested in that. This was our initial look at that data, and when we tried to scrutinize that data a little more carefully, we asked the question, because of the increased amount in the colorectal group, we asked, well, what do we have here?

So what you're looking at is a graph of a distribution plot by specialty with urogynecologists on the left and the colorectal surgeons on the right, and what you can see is a frequency. So the gray bars are the number of procedures performed at any given site by the providers of different specialties with, again, the colorectal surgeons on the right and the urogynecologists on the left. And when we did this analysis, it became clear to us that we had two outlier groups. If you look at the two highest bars on the left, they had relatively significantly fewer reported pelvic area pain events than any of the other urogynecologic or colorectal groups.

So when we then asked the question, was there a difference between the urogynecology groups or the colorectal groups after we removed those two outliers, we did not see a difference. When we then asked the question of those two groups as to speculations as to perhaps why, that's where the idea of perhaps the stretching came from. But there are certainly, as Dr. Fenner pointed out, other potential explanations. It could be observer effect, it could be patient-directed effects. We don't know.

DR. TALAMINI: Dr. Fisher.

DR. FISHER: So just one quick question going back to the stretching. Was the stretching done at all the urogyns or just those two?

DR. NIHIRA: No, sir, it was just to ask the question of those two centers as to what it was.

DR. FISHER: Okay, thank you.

DR. NIHIRA: Certainly. Then we moved forward to the question of performance. Could the frequency of the performance influence the prediction of whether or not there were pelvic area pain events? We're going to have to go two more slides forward now. Very good. So this is pelvic area pain. Okay. So what you're seeing now is a plot by number, by the sequence of performances. And certainly we've seen with other types of surgical procedures that as you increase the number of procedures, that you will increase the performance characteristics. I think what this plot is showing us is we did not see that to any significant degree.

The important thing to know is unfortunately we're talking about, in all of our data, relatively small numbers. But what you can see is, by those people who did their first and second, are the patients who had their first or second event, the third and fourth event, fifth and sixth event, seventh to ninth event, and then greater than the tenth event. In terms of the performer, it didn't make at least a statistical difference.

MR. BELOW: We were also asked a question about, of the patients that had ongoing pain, ongoing pelvic area pain, if any of those were related to infection adverse events. And the answer is no, those patients didn't have any incision site infection adverse events associated with those events.

To the last question about the patients with rectal prolapse, I'd like to invite Dr. Fenner to the lectern to discuss those cases.

DR. FENNER: So this is a slide that summarizes the -- there were actually four patients with five events. You see the first two patients are -- the first two lines there in that table are the same patient. So the first, she had had prior fecal -- had prior rectal prolapse. And so she had a recurrence and underwent a robotic-assisted laparoscopic rectopexy. And unfortunately, then she had a reoccurrence and she started feeling some protrusion. I felt that she had just an anterior rectal wall prolapse, and she's had two doses of sclerotherapy, and so she is continuing to be monitored.

The other patient with the recurrent prolapse felt something when she was bearing down, and she underwent an anterior rectopexy.

The de novo patients, one was felt not by the patient but by the clinician, and they obtained a defecography that showed some internal rectal prolapse. There's been no treatment since the patient is asymptomatic for that and it's ongoing.

And finally the last patient, she felt something the size of a grape coming out of her anus during the shower, and this was confirmed on a rectal exam by the surgeon. And then he or she performed a De Long procedure, which for the non-surgeons is basically an excision of the prolapsing rectum and reanastomosis. I guess to say that having the TOPAS in situ did not impact the ability to do the two most common procedures for rectal prolapse, that is, a transrectal approach or the laparoscopic rectopexy.

MR. BELOW: And thank you.

DR. TALAMINI: Thank you very much.

Does the FDA have any responses from this morning's questions?

DR. FISHER: Yes, I think -- Ben Fisher, FDA. I think we were asked a question about pain frequency and other patients that may be going through transobturator procedures, and I'm going to ask Dr. Long to address that.

DR. LONG: Yeah. I want to say thank you for bringing that up. Actually, we had an opportunity to briefly look at the TOMUS trial and basically the rate of patients with self-reported pain at greater than 6 weeks in that trial. It showed there was about a 2% rate with the retropubic group and the transobturator group who underwent mid-sling -- mid-urethral sling procedures was -- I'm sorry, it was 2% for transobturator group and 2.3 for retropubic group, none of which was statistically significant.

So I believe your question was sort of getting at the heart of trying to ascertain if some of the pain complex was due to the actual technique and some of the residual neurologic symptoms. This study did show that there were some associated -- there were slightly higher rates of transient neurologic symptoms with the transobturator approach. And again briefly reviewing the Cochrane review, in the mid-urethral sling procedures there was a higher occurrence of groin pain than in those who had transobturator procedures.

You know, as I said at the onset, I didn't have an opportunity to really dig in deeply to compare those numbers to what we saw in this study because we saw -- we have 50 AEs and 115 treatment-related. So obviously those rates are very different, and we would want to make sure we can compare them apple to apple. But we will certainly consider those moving forward.

The other thing I just wanted to add -- again, you brought up a very good question as

to whether or not there was any correlation with the pelvic pain AEs and the infection, and we looked really closely at those infection adverse events that were adjudicated as treatment-related and those abscesses.

So I did actually, in looking back through some of the information, see that there was one subject in whom there was a treatment-related infection with onset at 19 days post-implantation. That was their second AE. They went on to have several bouts of pain. In AE No. 3, they then went on to have urogenital pain. At AE 11 and at AE 13 had rectal tenderness, and that was ultimately one of the two unadjudicated AEs. So that rectal tenderness was ongoing at data closure.

I think that was -- those were the two questions that we were going to follow up on.

DR. TALAMINI: Okay, thank you.

So we'll now enter a period of probably about an hour, maybe a little bit more, for the Panel to deliberate. And I just want to make a couple of points. We're here as an Advisory Panel. There are two aspects to our advice. One are the official answers to these questions that we come up with and the votes. The other is the discussion that we engage in. So all of this is recorded. Part of the reason it's recorded is your comments, your questions, your thinking through some of these issues is just as important to the FDA as -- I don't know if it's just as important, but it's important in the context of what we're doing. So this is an important time.

Second, looking at the discussion questions, because that's where we're driving towards, you can see what the issues are, and they're not a surprise: effectiveness, safety, and a post-approval study. And if you look at the effectiveness, one question is going to be

discuss whether these results support effectiveness, discuss whether the results for these endpoints support the effectiveness. And for safety, discuss whether the pain -- discuss the pain and possible reasons for the pain, the safety profile, the prolapse issue.

So these are the things that we want to talk about for the next hour. If you have questions, issues, you can ask other Panel members whose expertise you now know. You can ask the FDA about their specific legal definitions. We can also ask our Sponsors, but that unfortunately has to come through me. I need to ask them to respond to questions that you may have. And we can also ask the FDA further data questions.

So with that said, yes, sir.

DR. HICKS: I have several questions. First of all, I'd like to ask Dr. Connor, from your standpoint, structure of the study, any problems that you specifically have with the statistical study?

DR. TALAMINI: And Dr. Afifi as well.

DR. HICKS: Right.

DR. CONNOR: No. I think given what FDA and the Sponsor agreed to, I mean -- you know, there's always challenges with single-arm trials. But given the trial and given the pre-established endpoint, I don't see problems with the execution of the trial or the statistical test used to test the hypothesis that was set out in agreement with FDA and the Sponsor.

DR. HICKS: Also -- oh, I'm sorry, go ahead.

DR. AFIFI: I also don't see a problem. But if I were asked the question at the beginning when the study was being designed, I would have advised that there be a comparison group, not necessarily a control group, because of the difficulty in getting a

control group. But not having a comparison group does put some doubt as to the interpretation of the results.

DR. HICKS: If I could finish, I had another question for the urogynecologists. In you all's experience with --

DR. TALAMINI: Well, if I could just -- let me just -- hold just for a second there, because I think I heard Dr. Fisher say that at the time of the trial design, there wasn't an obvious comparator group, but since then perhaps there is. Could you enlighten us a little more on that, please?

DR. FISHER: That is true. I think that Dr. Golding mentioned that we had a backup slide that shows what's been approved since the initiation of the study. At the time of the study, I believe that it was limited to the conservative therapies, which was pharmaceutical, dietary change, and biofeedback of conditioning the pelvic floor muscles, and we didn't feel that a sham group was appropriate to go through with no suitable benefit. So one of the questions that I'd like to put on the table is -- I'm sure that you all are probably familiar with some of the possible comparators that might be used now -- your thoughts on what would be appropriate.

DR. TALAMINI: I'm sorry, Dr. Hicks, I interrupted you. So please carry on. I'm sorry.

DR. HICKS: I had a question for the urogynecologists, just as a point of reference. With all the mesh procedures you all do, what kind of percentage are you looking at for patients that have pelvic pain, and is it similar to this? Does it seem way out of line or not?

DR. IGLESIA: Do you want to answer?

(Off microphone response.)

DR. IGLESIA: Okay. So there has been an evolution --

DR. TALAMINI: Name first, please.

DR. IGLESIA: Oh, I'm sorry. I'm Cheryl Iglesia.

There's been an evolution and a transformation in transvaginal mesh devices. When they were first cleared by the FDA in 2002, many of the devices had arms or legs, and they went through the transobturator foramen and ischioanal fossa, and so reported complications rates were double digits; let's just say 10% in terms of mesh exposure being the number one. But one of the more difficult ones to treat was pain. And so there are technical issues and how you tension it.

There are issues with the location and how these are placed in proximity to nerves, like the pudendal nerve and the obturator nerve, and the fact that it's going through muscles, because in the transobturator foramen you've got the skin, you've got your gracilis or adductor tendon. You're going to go through external obturator muscle, the obturator foramen, the internal obturator internus muscle, and levators.

And so I think that's my question about what is that baseline pain when you're going through this thing and whether or not some women have contractions. Because we also know, from ultrasound studies, there's up to a 50% decrease if you put a mesh in this size, but in vivo, it's going to shrink, and ultrasound shows that this can happen up to 50% shrinkage. And so I think that there are some patients who have greater inflammatory response. There's also new data on the interface between the connective tissue and the viscera and where the mesh lays and whether or not there's shearing effects. That's why I think the patients who are getting that physiotherapy or destruction beforehand probably

prevent in some degree contracture. I can't say for sure, but I think that there might be some basic science to support this, and some of that's been done at some big centers and some like in Pittsburgh. And some of the ultrasound studies have been done like in Australia. And there are other big centers around there, Oklahoma being actually another one of them.

So I think we have to learn from history. I think the impression is good in terms of that, but that is why the newer meshes do not have arms. See, the newer meshes are directly inserted into ligaments, and they're not going through -- they have -- they're not going through the arms and legs and those kinds. They're going through all the muscles and in proximity to the nerves and going through the ligaments. And I'm sure Susan has a lot more experience in this, as well.

DR. TALAMINI: Dr. Kalota.

DR. KALOTA: Susan Kalota.

First of all, the new mesh, as she said, is a little bit differently configured, so we're not going through the muscles, as she said. It's also a lighter mesh. I have not seen as much pelvic pain in the newer mesh configurations as in the past, but I'm still taking out mesh from before.

DR. TALAMINI: Dr. Kalota, perhaps you could define new mesh and old mesh a little more precisely for the record.

DR. KALOTA: Okay. The pelvic mesh, in particular AMS Perigee, Apogee, had arms, that the posterior repair came through the buttock as an arm. The anterior mesh came through the obturator foramen and -- now I'm blanking on the -- so there were four arms on

the anterior repair, two arms on the posterior repair. The current anterior repair and posterior repair go into the sacrospinous ligament only at the apex of the vagina and then prongs into the obturator muscle anteriorly, but less major arm stuff. But the mesh is also lighter, which may have an impact. It also doesn't have the length of time, and some of the mesh that I'm taking about has been in there 7, 8 years. So whether we'll see that in the future, an increase in the number of problems, I don't know, but the immediate problems less.

As far as removal of the mesh, if there's truly an infection around the mesh, there's not the ingrowth through the mesh, and what Dr. Fenner suggested about removing it might be correct. But if it's had ingrowth, there is no way you're going to get it out, other than dissecting it right on the mesh, all of the way through it. I wonder if some of the pain is not related to low-grade subclinical infection. That's a personal question. I don't know if we can get an answer to it. The other possibility is reaction to the substance of the mesh. Again my thoughts.

DR. TALAMINI: Yeah. Dr. Fisher, did you have a comment?

DR. FISHER: So yes. Ben Fisher, FDA.

So I don't want to stifle any of the discussion, any of the conversations, but I'd just like to remind everybody on the Panel that we're here to discuss this specific device, and we're not comparing it to anything else. This isn't trying to establish substantial equivalence against another device. I know that there may be some new, lighter things. And for those of you who are working in that field, I ask you to try to put that back in your mind right now, just so that we can really focus on the device that we have here today.

DR. TALAMINI: Dr. Faulx, on the phone, do you have a question or a comment?

DR. FAULX: Yes. Can you hear me okay?

DR. TALAMINI: Yes.

DR. FAULX: Okay. I just had a question for the FDA regarding since there isn't a comparator group, it's sort of hard for us to know, in looking at effectiveness, you know, without a sham -- which I understand why there's not a sham. But what is our option if we want to say that it appears that it looks effective, but since we don't have a control group, we can't tell? And do you guys think maybe there's something we could compare it to? Is there some intermediary between approving versus requesting further data based on a comparator? Or how would that work? Does that make sense?

DR. FISHER: Ben Fisher, FDA.

So once again, Dr. Faulx, the protocol was designed and the study was conducted, so we have to evaluate it against the results that we have for that. Where I think it might -- where our comparator might come in -- and we'll get into some discussions a little bit later -- is with the post-approval studies, either the continuation of the cohort that we have that's currently enrolled in the pivotal study, as well as the potential for a second study that would be conducted. But we're really not in a position where we can give a kind of approval. It's either approval or, you know, not approval. So, you know, we have to look at -- you know, we're relying on you guys to give us your input on how you feel about the efficacy based on the protocol design in the study that was conducted.

DR. TALAMINI: So following up on that, let me just probe our gynecologic surgeons and colorectal surgeons about the level of effectiveness that you're seeing in this study,

within the context of this field that you all know better than the rest of us, and the potential alternative operations that are out there.

Do you have a comment, Dr. Efron?

DR. EFRON: I think, compared to prior literature for any procedure that's been developed for fecal incontinence and the method of assessing the efficacy of the fecal incontinence, this procedure has demonstrated efficacy with respect to other published data, so whether it's an old procedure like the overlapping sphincteroplasty or a newer procedure like sacral nerve stimulation, in my opinion.

DR. TALAMINI: Thanks.

Sir.

DR. HICKS: Terry Hicks.

I think it's correct that if we're looking for incontinence across the board against all devices, that the mainstay that the bar would be set at is it 50% or not? That's where we are today, if you go to any clinical congress about it. Is there a 50% reduction in the problem or not? And obviously, from this effectiveness study, it shows that it actually beats that.

DR. TALAMINI: Dr. Kalota.

DR. KALOTA: I'm excited about the results. I think it's a problem that has very little treatment options at this point in time, and it definitely showed efficacy.

DR. TALAMINI: Dr. Iglesia.

DR. IGLESIA: So this seems superior, to me, to overlapping sphincteroplasty, but we have longer-term data on that with much larger numbers, which at best is 25%. You know,

it may look good initially at 50%, but over time, 75% of those are going to fail again, and it's because you've got a tear in a muscle and it's not well innervating. You just put two muscles together that are not well innervated. This is not going to function every time. It's just going to pull out or stretch out. It's probably a little bit better than Interstim, but again we have longer follow-up on that, and there are problems with the Interstim, which is direct sacral stimulation, and that has issues in of itself in terms of needing revisions and the cost.

So I'm excited about looking at the efficacy data. I'd like to be able to mitigate some of the consequences that can come with it in terms of doing the best practices in terms of who to train, how to train, and how to prevent some of these nonresponsive complications like the pain and/or rectal prolapse, which after they present, it doesn't seem to be as bothersome to me because it seems like half of those patients already had it. So that's a little better.

DR. TALAMINI: So another issue that we need to opine on are the sets of endpoints. And, again, as Dr. Fisher said, we're not going to redo this. The study is done. But in terms of the endpoints used, do you see weaknesses? Are you happy with these? Is one set of endpoints stronger than another, in your minds?

Dr. Efron.

DR. EFRON: I actually think the endpoints that were used by the study are quite good. They're very thorough. They look at objective measures and subjective measures, and those subjective measures are looked at with quality of life scores, which are as objective as you can get for subjective measures, right? So if you can follow that.

I think in looking at -- the best objective measure you have is the number of

accidents you have on a weekly basis, and that was clearly looked at. The Cleveland Clinic fecal incontinence score, Cleveland Clinic Florida, or the Wexner severity score has been validated with respect to quality of life, with 10 being the cutoff, which is why often we use 10 as the cutoff for fecal incontinence with that score. Because if you're above 10, that is significantly impacting your quality of life. And if you're below 10, that is your quality of life is not as impacted.

And so with a significant reduction in the score to below 10, that there are also some objective data there. And everything they looked at, I think, as far as outcomes for fecal incontinence, it's great. What I'm still a little confused about, which goes to the next question, I guess, a bit is safety. Were the patients screened for pelvic pain beforehand? I still don't have a good feeling of who was screened for pain and who wasn't and how many of the patients had suffered postoperative prolonged pain. Did they have preoperative pain?

DR. TALAMINI: So we'll hold on that, and let me get, Dr. Hicks, your opinion about the endpoint strengths, weaknesses, happiness, unhappiness.

DR. HICKS: I'm happy with the endpoints. And, again, the Wexner scale has been, over 10 years, proven to be a solid instrument. I may have misunderstood, but I thought there is information in the packet about them, were people with pre-implant pain. I think it was like 35, 33%, somewhere in that range, if that's correct.

DR. TALAMINI: Do the Sponsors want to respond to that question?

MR. BELOW: Yes, that is correct. So if we could pull up the demographics. Yes. At baseline, we had 55% of the patients that had a prior history of pain.

DR. TALAMINI: Okay. Other thoughts on the endpoints, Dr. Kalota?

DR. KALOTA: I was comfortable with the endpoints.

DR. TALAMINI: Dr. Iglesia.

DR. IGLESIA: Yeah, I think that they had really good objective and subjective validated questionnaires that they were using on this. I think the things that I would've liked to have seen is a little bit more imaging. I mean, there were some subsets that did get the dynamic cystoproctograms. In this particular -- which may be helpful when looking at the anorectal angle. But in this particular -- with this device and with the synthetic mesh, actually probably the imaging modality of choice would have to be ultrasound and transperineal, and it doesn't have to be the fancy 3D beam -- because not everybody has that.

Because I'm just concerned, knowing what happens with vaginal mesh and what happens with the transobturator, that sometimes where you place it, it is not where it's going to end up over time, and things can either work its way in, work down, work below, and we know to angle it. And so if there is a way of making sure that's in the right place at the time and that it's not moving, that might be useful because that might be relating to some of these issues with why people are developing pain. I'm not sure.

The other thing was the question that was brought up by the FDA on the defecatory dysfunction, you know, whether or not the CRADI and the PFDI are useful, but they don't really answer about how difficult it is to evacuate. But at the same time I'm not 100% certain I know what the best -- maybe Dr. Efron would know what the better questionnaire would be for that.

DR. EFRON: No, I don't have a better questionnaire. I agree with you that I think some of the pre-therapy radiologic tests can be quite difficult in someone who has significant fecal incontinence because they can't perform the maneuvers we need to actually measure the anorectal angle. So it can be quite frustrating. Perhaps if assessment of the puborectalis through ultrasound would be a better technique. I don't know what Dr. Hicks thinks.

DR. IGLESIA: I mean, I'm just saying, if they think that the modality of the mechanism of why this is working is that it's replacing, like a sling would replace a pubourethral ligament and this will replace a puborectalis muscle, maybe those 31% who failed really have lousy, you know, muscles to start with. And even though you replace this, you're not going to be able to replace it to the extent that it's needed to replace that angle. And I'm just trying to refine this so that women get the best outcomes. You know, I'm not saying that this shouldn't be approved or cleared or whatever. I'm just saying, if we're going to do it, let's do it the best way we can to avoid complications and to give them the best results. Clearly, there have been some homeruns here from some of these people who had clearly outstanding results in the right hands and the right patient selection.

DR. TALAMINI: Dr. Afifi, you had a question or a comment?

DR. AFIFI: Abdelmonem Afifi.

Yeah, I do have a question. In terms of the pain pre and post -- so get the percent who had pain pre and the percent who had pain post, fine. But another standard way that is done statistically is to do the correlated proportion table, where the two columns are pain pre, yes/no, and the two rows are pain post, yes/no, and then you have that 2 by 2

table. I wonder if the Sponsor made that analysis or whether that could be done right now so we could look at it.

DR. TALAMINI: Does the Sponsor have a response?

MR. BELOW: We have the data. We have not done the analysis to look at that correlation table of pain pre/post, yes or no, as a correlation table. It's certainly something that we could do and provide for you.

DR. AFIFI: Do you think that could be done today?

MR. BELOW: Yes, we could do that today.

DR. AFIFI: Okay, thank you.

DR. TALAMINI: Dr. Connor.

DR. CONNOR: And in terms of your endpoint question, 5 or 6 years ago I was here with Oceana's Solesta device, and so just getting at -- you know, overcoming the fact that we lack a sham or we lack a control group. And that trial was just a 6-month $Responder_{50}$ endpoint. I pulled up their FDA label because it got approved. They had 53% on their device, and only 31% on sham. So it seemed like the same, you know, patients who failed conservative therapy. I don't know exactly how analogous it is, but the fact that, you know, that sham group had a 31% response rate. In terms of efficacy, this is a lot better and probably more better than any slight differences in, you know, the patient populations might contribute to.

DR. TALAMINI: Yes, we have had some adventures with sham trials, there's no question.

If I could ask our three public members if you have comments about the

effectiveness that you've seen from both presentations, our Sponsors and the FDA.

Yes, ma'am.

MS. BERNEY: Well, as a patient who has long suffered with this problem as a result of having two very large children and 10-pounders and loads of damage and a badly botched hysterectomy, I can tell you that anything that gives better than 50% seems effective to me, and I would love to be able to do that. The number of adverse events is concerning to me because, as a person who also suffers from continued pelvic pain without resolution, that's a very difficult thing for women. On the other hand, after listening to the personal stories, if you were to ask me do you think that this is worth doing, I would say yes, because if it gives more than 50% improvement for those people that it works, then it's worth the risk.

DR. TALAMINI: Thank you.

Dr. Fennal, comments on effectiveness?

DR. FENNAL: Mildred Fennal.

I'm going to agree with everyone that any type of effectiveness for someone suffering would be very good. It just seems 50% is just half, and I know that this is already done, but I would like to see more, because I think 69.1 is just a D instead of a C, and I'd like to see a C, but that's just me. So I do agree that what has been presented, 50% is better for the women who feel so secure and so much better about what has happened. The only other thing about the endpoints is I would like to have been able to hear from some of the subjects that it did not work for.

DR. TALAMINI: A good point.

Dr. Donatucci.

DR. DONATUCCI: Just one comment. I am not familiar with the secondary measures that you mentioned earlier, the CR --

DR. IGLESIA: The CRADI.

DR. DONATUCCI: Those two. What I noted when the Sponsor presented this morning is that those two have minimally clinical important differences established, and what struck me is the three-and-a-half to fourfold margin over that minimal difference that was observed in the study in terms of efficacy.

DR. TALAMINI: Dr. Inge.

DR. INGE: I want to take a slightly different tack here and applaud the FDA for their diversity in thinking of having a pediatric specialist on the team, because we take patients with anorectal malformations in teenagers that have incontinence after really, you know, either difficult operations or unsuccessful operations for some reason as babies. And so I guess I would just challenge you all to think differently about this effectiveness question, and to say if somebody's having 30 episodes in a 2-week period and you get it down to 20, is that a loss? Is that not a win as well?

DR. TALAMINI: It's a good question.

Dr. Connor, did you have a comment?

DR. CONNOR: Yeah, I was just going to say, so I appreciate and agree with your comments, and I'm going to ask you something as a patient later. But I also think we need to think about bias. And I'm extremely grateful that the patients come and tell their stories and I see the benefit. But I also realize that someone in whom it didn't work probably isn't

willing to get on an airplane for the reasons that they discussed, but also patients who have a lot of pain may not be willing to travel. So I think we're definitely getting, you know, a biased sample there that we just need to keep in mind.

DR. TALAMINI: So I'm sorry. Yes, ma'am.

MS. BERNEY: Barbara Berney.

I do have one more thing I want to add, and it was brought up several times, that this is a subject that many women are reluctant to discuss. It took me 12 years to talk to my doctor about it, and when I did, I was told, oh, you have irritable bowel, wear a diaper. That doesn't help me. So I'm excited about something that would reduce by half the couple of accidents I have. I mean, for me, that would mean that would be half the time I would have to calculate is there a bathroom where I'm going and how far away from me will that bathroom be?

DR. TALAMINI: Thank you.

Yeah, Dr. Fisher.

DR. FISHER: Two things. One, I just wanted to get clarification on the imaging, as to if the imaging was pre-procedure, during placement, or post-procedure.

DR. IGLESIA: Well, I was thinking about the --

DR. TALAMINI: Name, name.

DR. IGLESIA: Cheryl Iglesia.

Pre-procedure, I just would even like -- because in Michigan they have one. Dr. DeLancey is the guru on pelvic anatomy and has probably the largest collection of pelvic MRIs that are dynamic, and that would be very interesting to look at levators that have

been avulsed and how this would work in that kind of population. I understand that that's probably really expensive, but maybe in something looking at a subset, because I'm looking at those who fail. At the same time, the tensioning and where this is located, it seems like everyone gets it at the right spot. And, you know, I haven't done this procedure, but it would be nice to see where it sat, even if it was not maybe intraoperatively but soon or relatively after the surgery, that you just get a spot because you can really see mesh pretty easy on transparent ultrasound. We use it a lot now in terms of guiding us for mesh removal.

So anyway, as a subset, just to see what's going on long term because there seems to be a little bit of a drop off, I mean, even when we account for intent to treat, there is a little bit of a drop off, and I'm just wondering, is it because the mesh is moving? You know, is it staying in the right position? And I'm not certain, but I know that that's probably happening with one of our transobturator approaches.

DR. FISHER: Right. The second comment was kind of something that Dr. Connor touched on and that was -- and also it has to do with kind of patient preference, in that you have these women who came before us today saying how this has really changed their life. And the one thing that I wish that I had done, kind of an unorthodox approach, would have been to ask them, did you experience pain or have you -- are you still experiencing pain? And if you are, do you feel the gains are worth that?

DR. CONNOR: Right. Jason Connor.

Yeah, that's one of the things I will ask Barbara later, but I wish I could've asked because, yeah, I think it's going to come down to how much pain is worth it. And I get that.

You know, I may be willing to suffer pain and still go to a graduation and still go to a wedding, but I won't do those things if I'm experiencing incontinence. So I think it would be really beneficial to me to understand how much pain is worth the decrease in incontinence. Yeah.

DR. TALAMINI: So with that, let's turn a little bit towards the safety issues, and you can see in your discussion questions that there are three categories. It's pain, as we're already discussing, prolapse, and whether the safety profile of the device that you've seen both today and in the materials forwarded to you indeed adequately describes the profile for the intended population. Those are sort of the three things that we need to get to.

So I think, Dr. Connor, that's a beautiful -- you know, you're putting the point right on it. How much pain is worth it? It sounds like it's greater than zero, but who knows what the number really is.

DR. CONNOR: Right. So I'd like to address that question -- Jason Connor speaking -- to Barbara and then to the docs who see these patients, if they have a sense of, you know, how much pain is a woman willing to tolerate to decrease her incontinence.

MS. BERNEY: I've seen some things in my life.

DR. CONNOR: Yeah. So my question was -- it sounds like a woman who's experienced both, you know, pain and incontinence issues -- is how much pain would you be potentially willing to tolerate afterwards, or the risk of pain? You know, if your doctor was saying there's this new device that can decrease incontinence but some patients experience pain, I assume I would be willing to trade off some risk of pain for a decrease in incontinence, and I was just wondering if you could help me and us understand, as a

patient, what that tradeoff would be for you.

MS. BERNEY: You are correct in assuming that I would trade off pain for having to wear a diaper and run to the bathroom every so often. For most people, they can take pain meds. I'm one of those unfortunate people who cannot take any kind of opiate medicine or I will die. So for me, I just live with it. Most people don't have to do that. They can take something for the pain. So even if they have to take something for the pain, the fact that they are not having accidents which smell bad, look bad, most women, I think, will think that it was a bargain.

DR. TALAMINI: How about comments from the clinicians that deal with folks with this problem?

Dr. Iglesia.

DR. IGLESIA: Cheryl Iglesia.

So that's why I kind of wanted to read that TOMUS, that transobturator data, because it looks like the baseline pain rate is about 2% for neurological symptoms and whatnot. And in this trial, while they said 23% of people had some pain, the large majority of that resolved, and it's only this 5% that had this persistent, nonresponsive pain, and that patient felt like she was sitting on a rock. That would probably be really a bad tradeoff for, you know, being fecally continent.

And so my -- is just try and do whatever we can to not let that happen and minimize that. If 5% is the best we can do and you're trading that off for a 69% overall improvement rate, then maybe most people in the decision-making process would accept that. But if you happen to be that 5%, you know, you could be extremely disappointed too. So whatever

we can do to try and identify what those risk factors were, and it seems like it's just a small number, I think the only way we're going to be able to get this kind of information is going be through postmarket surveillance and obviously with a comparator group of some sort.

DR. TALAMINI: Other comments?

Dr. Kalota.

DR. KALOTA: Susan Kalota.

I think the bottom line is that this is a terribly debilitating disease, and women would trade an awful lot for that. So, for me, the pelvic organ prolapse is nothing compared to incontinence. I cannot see that as something -- if I told a woman that might happen to her versus she might be dry or have substantial improvement, I don't see that as an issue at all. The vast majority of women would easily trade prolapse for continence. Pain-wise, I think it gets back to Dr. Connor's comment, how much pain? And many people would trade some pain for continence. So it's just how many are in the debilitating, god-awful pain? That didn't seem to be a huge number.

DR. TALAMINI: Dr. Efron, do you agree?

DR. EFRON: Jon Efron.

I agree, I do agree. I think one thing we have to keep in mind when talking about pain is yes, if you trade pain for continence, you probably wouldn't be happy if you were still incontinent and had a significant increase in your pain. So we have to remember that.

I do think that the organ prolapse -- I, in my mind, don't relate that as a result of the intervention of this procedure. That is probably more of a continuation of the overall disease process that's taking place, in my mind, with patients that have severe fecal

incontinence. And I think that the events that occurred, specifically with the rectal prolapse, were in patients that already had had some prolapse, and we should note that the recurrence rate for rectal prolapse procedures over a period of time is quite high, 70% almost for the perineal procedures that were described and up to, in some studies, 50% for abdominal procedures. So I think it's hard to equate a timeline with this intervention and the rectal prolapse that's taking place.

DR. TALAMINI: Dr. Inge.

DR. INGE: One of the questions that comes up, you know, that we haven't addressed on this pain issue is management of the pain. So is this something that requires that a woman would consider it so significant that she would even go to a interventionalist to have a nerve block or, you know, look for a selective treatment of it? Or is it something that's so mild and general, other than the sitting-on-the-rock problem, that you really wouldn't even go that distance?

And then the second thing is on the issue -- somebody hypothesized that maybe it's low-grade infection. Has anybody done any white cell scans or any special testing to look for subtle signs of infection?

DR. TALAMINI: Yes, Ms. Berney.

MS. BERNEY: Barbara Berney.

Well, having suffered for many years with chronic vulvar vestibulitis where you can't sit, you can't stand, you can't urinate, you can't anything and it's misery, as well as triple prolapse, which was supposed to be fixed and was botched, I can tell you that I would still rather have the surgery so that I wouldn't be having fecal accidents. I mean, I agree with

Dr. Kalota. You can hide prolapse. It's annoying, it's difficult, and you know, wetting your pants is not nearly as difficult as defecating in your pants. So from the patient's point of view, I would say that fecal incontinence is probably a bigger problem than prolapse, and that from the women I know who've suffered the same sort of thing -- we have a support group -- they agree with me.

DR. INGE: From the Sponsor, though, has anyone done any sort of pudendal block in an effort -- do a test block even, not trying to do an ablation or something that's permanent, but --

DR. TALAMINI: Yes, go ahead, please.

MR. BELOW: Paul Below.

We did not have any of those studies done as part of our clinical trial. No.

DR. TALAMINI: Dr. Hicks.

DR. HICKS: You know, there's a little bit of common sense that we have to use here too, and if you think about it, you know, if the patient is really informed about this percentage of pain that could occur, the patient can help make that decision. That's a patient decision. We do it all the time. If you've got people who get back surgery, it may not be perfect, you may have pain. People get their hip done, you may still have hip pain. If I could get mobile and get moving again, I'll do the hip surgery, I'll do the back surgery, I'll do whatever surgery. So I think that the main thing would be the common sense. That the patients are informed of this is the important factor.

DR. TALAMINI: Dr. Fennal, please, first.

DR. FENNAL: Mildred Fennal.

I just want to make one comment on choosing the procedure over pain. When people are informed, they aren't -- women aren't informed that you're going have some pain. Now, impersonally, the only thing I can compare it with is taking care of women who have had surgery similar to that in that area. And for the 72 hours after they've had the surgery, if you are caring for them, when you wake them up, it's if I had known that it would hurt this bad, I never would have had it done. So we do have to consider that. And so I guess I'm asking -- maybe asking a question, look at managing it better, even when you're giving the opiates in the beginning. You need to help the nurse some. It's very hard to watch those women suffer from that type of invasive procedure.

DR. TALAMINI: Thank you.

Ms. Berney.

MS. BERNEY: I would like to agree with Dr. Hicks. Having had a hip joint replacement and still having some hip pain, I can tell you that I am ever grateful that I had it done. And, in fact, I went 15 hours after surgery with no relief of any kind. And I'm having another one done in April. So what does that tell you?

DR. TALAMINI: Thank you.

You have in front of you a set of questions that we didn't initially have with respect to labeling that we should -- I'm sorry, Dr. Fisher.

DR. FISHER: Yeah, just real quick. Before we go to labeling, I want to go back to pelvic organ prolapse and just ask, very quickly, it would appear that fecal incontinence, urinary incontinence, pelvic organ prolapse may have the same etiology. Your thoughts on is what we saw in POP, is it due to the procedure? Is it due to the same underlying

etiology? Just real quick if we could.

DR. TALAMINI: Dr. Kalota.

DR. KALOTA: My thoughts on that is, that having a comparison group, if we could, that have no intervention, to look at that. I think that would tell you -- if you could get a comparison group, it would tell you whether it's related to the problem or the treatment.

DR. TALAMINI: Other thoughts? Dr. Efron, probably the pathophysiology or a separate issue?

DR. EFRON: Well, I think, as far as the rectal prolapse goes, it could be potentially part of the pathophysiology. I don't think it's necessarily a related procedure. We don't quite know what causes rectal prolapse. The etiology of it is unknown. So, you know, whatever. We're still struggling with that. And I think even with a comparison group, given the small numbers, it would be quite hard to show that there was a causative effect.

DR. TALAMINI: Yes, sir, Dr. Hicks.

DR. HICKS: I have to ask the urogyn people again. But if you look at the data, as I remember, 1 in 10 women, by 80, have a prolapse procedure.

(Off microphone comment.)

DR. HICKS: Yeah. Yeah, it's a lot. So if you just took a group of people off the street and follow them through, this would be probably below the standard.

DR. IGLESIA: I definitely think, Dr. Fisher, that it's related to pathophysiology. The major risk for pelvic organ prolapse is going to be childbirth and delivery. The same thing for fecal incontinence. The question is, what is the added risk of getting de novo incontinence after you place this fecal sling? And, again, you would need that comparison

group, whether it be something done with a registry and someone who's getting the pessary, if you have a pessary arm in there. Maybe even include the Eclipse arm. I don't know. We'll probably have that discussion later. But clearly these women already have that risk because they have pelvic floor trauma. One delivery increases your risk for a prolapse fourfold. And then if you end up having a episiotomy tear, you know, all bets are off at that point.

DR. TALAMINI: So there you go, Dr. Fisher.

DR. FISHER: Thank you very much.

DR. TALAMINI: So turning a little bit to the labeling, you can see two broad categories that we will need to opine regarding. The first is the specifics in the labeling: pregnancy, age restriction, other interventions, and the second are the training issues. So first let's turn to pregnancy, age restrictions, or other interventions that might have occurred prior that you think should or should not be part of the labeling for such a device, were it to be approved.

Dr. Iglesia, do you want to render your opinion?

DR. IGLESIA: Yeah. In terms of pregnancy, as we know that this is a risk factor, you know, most people would generally tend to have women wait until after they completed childbearing to undergo a permanent implant such as this. It would just make common sense. That being said, there are people -- we say the same thing for people who have suburethral slings, and we have studies that have shown that women have gotten pregnant because urologists and urogyns haven't told them that they shouldn't be getting pregnant. And the study that came out of Kaiser didn't show that it actually made that much of a

difference. I wouldn't want to risk that after you've gone through this type of surgery. So I generally would probably counsel let's do this afterwards and let's really work on the medical management, maybe even using some of the new devices, the Eclipse and stuff that we have. But definitely biofeedback, fiber bulking, Kegels -- all of that jazz.

In terms of age restrictions, this is a very interesting study in that it seemed like the older patients did well, which is very kind of untrue. Like Interstim people, the older age actually was a risk for failure. So I don't really -- gosh, it ranged from 30 to 80. You know, now 80 is the new 60 anyway. But I don't know if I can necessarily recommend an age restriction for that.

Anyway, do you want me to go on with the last one, too? Should prior labeling in terms of having prior surgery for this? I mean, this is sort of a last resort for people who failed other things, including prior overlapping sphincteroplasties. It does seem like some people who failed this, though, did end up getting the neuromodulation, Interstim, so that didn't preclude that from --

DR. TALAMINI: So would you agree with the labeling as you see it there in the paragraph?

DR. IGLESIA: Yes.

DR. TALAMINI: Dr. Kalota.

DR. KALOTA: Susan Kalota.

I can't imagine doing the surgery on a pregnant person. It just doesn't make sense. And I don't think I would preclude it from someone who might get pregnant in the future. But given that you're going through the obturator fossa, I would not want a patient to do a

vaginal delivery after this. It seems to me like it would put too much stress on things and potentially cause an erosion. But doing a C-section, it seems like that would be a reasonable mechanism of avoiding any trauma to the surgical field.

DR. TALAMINI: Dr. Hicks, your thoughts on the labeling issues here?

DR. HICKS: I'll have to bend to the urogyns about the pregnancy issue because you had experience with that. One of the questions I wanted to ask, though, if I could, to the urogyns is, from the time of implant of -- your experience with meshes -- until you see an erosion, what kind of time frame are we looking at? Because we've studied these people for 3 years. Is it shorter than that, longer than that?

DR. IGLESIA: You know, if it's -- if your mesh is implanted too close to the surface, you're going to see an exposure. The erosion issue is the thing that can work its way in, and that's what we don't know about. And whether it's the tensioning or whether it's transmural and just kind of like in the detrusor or in the body, the rhabdosphincter of the urethra, and then over time, it works its way in.

Because you did a cysto and you didn't see the mesh as you were putting this in, but it's worked its way in, that's why we need these postmarket studies to find out what's going to happen. That's why maybe even imaging to see where is this -- if this is moving, because your pelvic floor is not -- it's a mobile thing. Things are going in and out. You know, you're moving. So there's dynamic forces that can work either positively or negatively, I guess. The second thing is, with aging, understand that the vaginal epithelium has -- you know, there's the epithelium, the musculus, and then the adventitia that with menopause, that stuff shrinks really significantly, and women aren't using estrogen, and what happens over

time, we don't know. But clearly I've had cases where a mesh was fine and now, you know, 10 years later we're seeing it in the bladder. We're seeing little -- and it's starting to work its way in. So I think we have to, you know, proceed with a little bit of caution and understand that we don't have a lot of data on long-term implants.

DR. TALAMINI: Dr. Fisher.

DR. FISHER: So we're on to the subject of erosions, and we talked about that briefly this morning, and the comment that was made was that we haven't seen any erosions. But what I would like to do, if it's okay with Dr. Talamini, is to ask the Sponsor if they could provide some clarification to the Panel on what was required by the protocol, what was collected and how when it came to erosions, because that cohort is still ongoing. So if we might be able to get some clarification from the Sponsor on that.

DR. TALAMINI: Could we prevail upon the Sponsors to address that for us, please?

MR. BELOW: Yes, thank you. I'd like to invite Dr. Nihira to the lectern to address the methods that we used in the clinical study to detect erosion.

Dr. Nihira.

DR. NIHIRA: The issue of erosion is a big concern. But as somebody who unfortunately takes care of a lot people with mesh erosions, palpation generally is the most sensitive way that we've been able to find it. And certainly by palpation, that was not shown to be a concern into the vagina or the anus or rectum.

DR. TALAMINI: Dr. Fisher.

DR. FISHER: So just a point of clarification. Now, I don't believe that the trial itself required a thorough examination to look for erosion.

DR. BELOW: The mesh-related complications, including erosion, were specified in the protocol of adverse events for our investigators to actively surveil. We didn't define any specific techniques within the protocol by which the investigators would do so. We left that up to standard of care assessments and individual judgment of the investigators.

DR. FISHER: Right. So I understand that yes, you did that, you went back and looked at the records and that there is still a cohort of people that are willing to do a more thorough investigation or check at a different time point. It's still something that we could assess.

MR. BELOW: That is.

DR. IGLESIA: And then there's -- excuse me.

DR. FISHER: I'm sorry. I was going to say, actually, I think the data has been specified in the protocol for the extended cohort.

DR. TALAMINI: Dr. Iglesia.

DR. IGLESIA: Then with that trial, as you lose people to follow-up, we don't know what we don't know. If people have had this but they're no longer in the trial, how do we know that they haven't gone to somebody else and have a complication? You had a pretty good follow-up, but still, what were there, 17? So it was over 10% that were lost, that were classified as failures. But I'm just wondering, of that 10%, 11%, did any of them have a complication? We don't really know.

DR. TALAMINI: Dr. Hicks, you had a thought from before?

DR. HICKS: My concern about this is just historically, if we look at mesh implants and when they were approved, everything looked great, and now look where we are, okay? You

know, social media, litigation, issues like that. I was just trying to find out what a comfort number was that if I could sign my name to, that we followed it far enough out to make sure that's not going to be like the other mesh products. You know, I'd hate to be -- you know, that we didn't look at 5 years or 6 years, then suddenly it becomes a monster problem.

DR. TALAMINI: Dr. Kalota, do you have a thought?

DR. KALOTA: I have a couple of thoughts. I think the previous mesh is that the studies weren't done, so each individual person had their own single-person study to find out who was appropriate. And we've got a study here. Definitely, we need larger numbers. As far as vaginal mesh, in my mind, clarification of extrusion versus erosion. This extrusion is exposure in the vagina. We shouldn't see that with this. And that, palpably, you can feel it with exam. I would think that you could feel erosion into the rectum, if it's clinically significant -- and I agree that sometimes we did -- when you do the cystoscopy after a sling placement and see no mesh in the bladder, if it's attached going through the detrusor muscle with time contraction and expanding, you may seesaw that and get into the bladder, and in the bladder you have blood and stones and stuff. In the rectum you wouldn't have that. But I would still think that if it was a clinically significant erosion into the rectum, there would be symptoms, whether it be bleeding, pain, something that you could palpate.

DR. HICKS: My question was not about -- my question was the length of time, whether that could occur or not. You know, does it happen at 6 years and suddenly you've got -- you've put in thousands and there's the issue? That's why I was asking you all about -- experts in mesh, and some of you said it's almost 10 years, whatever.

DR. KALOTA: Yeah.

DR. HICKS: And so I was just trying to get a timeline for how long it would take. I mean, you could certainly find it. The question is how long is it going to take?

DR. TALAMINI: And that is a key question because, again, how long are you going to hold off approving or not approving and somebody waiting for those sorts of really long-term questions to be answered because they're unknown?

Dr. Kalota.

DR. KALOTA: I think you're going to see some right away, especially with the extrusions in the vagina. The injury to the rectum, I think you're going to see most of it early. But yes, you can have things that occur with time, as it shrinks and puts more pressure.

DR. TALAMINI: So let's, if we could, turn to the training issues a little bit here. And the questions brought forward are the differences in specialties, urogynecology and colorectal surgeon, in terms of adverse events and what that may or may not -- and I realize, you know, I'm getting close to the third rail here, but what the implications may or may not be in terms of training or other issues. But specifically I think the question is, do the training paradigms that you've heard this morning, are they sufficient? Are they appropriate? Do they feel right in terms of labeling, or are they too much, too little?

Dr. Iglesia.

DR. IGLESIA: Cheryl Iglesia.

So I do think, again, this is one where we could learn lessons from history because some of the problems with the first generation of vaginal mesh was maybe the marketing

was ahead of the science a little bit, and we didn't have as stiff criteria on who gets training, and you have to go through those modules, you have to do a simulation, and in this case you are being proctored, and that wasn't the case when actually slings and meshes -- if we be honest with ourselves, people would just go to a weekend course and have three cases scheduled for the next Monday. So I applaud the company for, you know, taking that step.

I still worry, though. This kind of data cannot be extrapolated to your average surgeon. So these 150 patients were done at big centers with high volume, and we know that, you know, volume, whether it be the private practice group that do the high volume or these academic centers, definitely impacts your outcomes. So, yeah, for some -- I mean, the two seems slow to me, I mean low to me, but I think it depends on patient -- of the surgeon's previous level of skill and experience. I think that has to be taken into account.

DR. TALAMINI: What number doesn't seem low?

DR. IGLESIA: What number doesn't seem low? I mean, I know it wasn't statistically significant, but once they did 10, they seemed to be okay. But, you know, I know that, for like slings, people say you need to do like 25 to get on the learning curve. If you're doing eight a year to stay on the learning curve -- you know, this is sort of like I think there are people who could do two and they're expert, and then there could be two people -- there could be people who do 20 and they still can't get it.

DR. TALAMINI: The FDA is looking for your advice, though.

DR. IGLESIA: Yeah. I think, in addition to going through the learning modules, being board certified or whatever, and doing the proctoring and doing the maintenance, I do think that you should take into account that person's skill, like how much pelvic reconstructive

surgery are they doing.

DR. TALAMINI: Dr. Kalota.

DR. KALOTA: I don't think the company can take that into consideration. I like the idea that they're limiting who can do it. I think the fact that if they're staying with urogynecologists and colorectal surgeons, they're probably going to be more skilled in that area. I think that proctoring, too, is reasonable. I don't think you can reasonably get someone to proctor many more than that, but there is probably going to be a learning curve. I would hope that part of that learning curve is the other mesh procedures one has done.

DR. TALAMINI: Other Panel members have thoughts about numbers in the training protocol?

Dr. Hicks.

DR. HICKS: I just wanted to say that, Dr. Iglesia, you're right on it. The FDA approved, without naming the product, the product was approved, and then it went out into practice, and everybody wanted to try and use it. The papers that were written by people that were skilled in the area of this utilization produced tremendous results with tremendous papers. But those who didn't routinely work in that area, which was the anorectal area, ended up with just horrible complications; it was unbelievable. And it was based on, more than the number you did, though, about people's experience in the area. So it really is so important if you get somebody who does this all the time. So that's why you can't put a number on it unless you put a grade, skill experience versus numbers.

DR. TALAMINI: So would it be your advice for somebody to be evaluating

somebody's practice, to say whether it's appropriate for them to be putting this in or not?

DR. HICKS: I don't know the logistics of how that would work. You know, in the best world scenario it would be, yeah, you watch them do them and you sign off on them.

DR. TALAMINI: Dr. Efron.

DR. EFRON: Jon Efron.

So I think if you break the procedure down into its two components, the first component is the perianal incisions and the placement in the post-anal space or the area around the rectum. I think, from a colorectal surgery standpoint, most colorectal surgeons would feel very familiar with that. I think if you look at passing a big sharp needle from the top down to the bottom where lots of bad things could happen, many colorectal surgeons may not have the experience that urogynecologists have in passing the obturators to bring the mesh through. So I think that maybe, depending on the specialty and the experience of the individual, some cadaveric training on the day -- more cadaveric training maybe on the passage of the obturator may be helpful.

DR. TALAMINI: Yes, Dr. Iglesia.

DR. IGLESIA: Cheryl Iglesia.

Okay. So if you proctor for two, it's not just proctoring and you did two. You have to do it successfully. And then, secondly, I think in order to be -- do the best for our patients, anytime you're putting these in, maybe on the initial phase it should be scrutinized through a registry so that people can follow it. I mean, if there are people who are having consistently higher complication rates and all their patients are getting pain or they're having abscesses and whatnot, then those are outliers and will need to go back into the

training. So that's why I was mentioning that PFDR, because we have that mechanism of a registry kind of built in for postmarket surveillance after this is approved, I mean. And then we can -- I don't want to stifle innovation, and this sounds like a great thing. At the same time, I think there is potential for harm.

DR. TALAMINI: Dr. Connor or Dr. Afifi, are there any hints in the numbers as to how many would be the right number to proctor?

DR. CONNOR: No.

(Laughter.)

DR. CONNOR: I mean, I think from this data, that's hard to do, but yeah.

Dr. Afifi.

DR. AFIFI: I think if I were to do this operation on myself, I mean, have it done, I would go to a urogynecologist.

(Laughter.)

DR. TALAMINI: Dr. Efron.

DR. EFRON: I have to say, Jon Efron, in defense of the colorectal surgeons --

(Laughter.)

DR. EFRON: I mean, let's just remember that when we broke down the pain data to some extent, it wasn't so much who was doing it but whether they were doing specific relaxation exercises beforehand. Now, that's all very small points and very small data, but all of this is. So I'm not so sure we can make determinations based on this data, and Dr. Connor is going to disagree with me, I'm sure, but based on what we are seeing in the study as to who should be doing it and who shouldn't be.

DR. CONNOR: Jason Connor.

So no, I totally agree, and I think the breakdown, to the extent that I can multivariate model it in my head, I totally agree, there's not a difference in colorectal surgeons and gynecologic surgeons. There's a difference in who stretches and who didn't. So I think when we get the post-approval study, we should formalize the role of stretching maybe in the post-approval study.

DR. TALAMINI: Dr. Fisher.

DR. FISHER: So we're going to have to leave labeling and go to the post-approval study. But before we do, I don't want to skip this, I want to get your thoughts. Real brief. Indication for use, 18 and above. Population studied, 32 and above. Any special concerns about the population from 18 to 31 that we need to take into consideration, either because they are who they are or something that we need to put in the labeling?

DR. TALAMINI: And because the mesh is probably going to be there for a longer time.

Yeah, Dr. Efron.

DR. EFRON: I do think we have to put on the label that this may interfere with their ability to have a vaginal delivery with pregnancy. It's something that definitely needs to be brought up.

DR. TALAMINI: Others? Dr. Kalota.

DR. KALOTA: I would agree with that. I think 18 and above is very reasonable. I don't think it should say that they're buying a no pregnancy for life clause, but that it should, in my mind, be labeled that they may need a C-section.

DR. TALAMINI: Okay. Dr. Faulx, I don't want to pick on you on the phone, but if you have something you want to add to the deliberation, please chime in.

DR. FAULX: I have one comment actually, which was regarding the numbers issue, which I know is not the part that we are on anymore. But, you know, GI as well as surgery, especially in training or an acquisition of new skills, is really getting away from numbers because numbers don't say, you know, because you did 100 colonoscopies that you're good at doing a colonoscopy. So I think some sort of metrics of looking at maybe, you know, doing the training, doing a post-test, you know, something like that versus doing discrete numbers and having them watching them do it on a model or something like that. Maybe even a written -- you know, written questions. You know, things like that might be more reasonable than actually putting a number to it, because I think people bring different skill sets, as they were talking about, to this. And so certain people can do it in 2 and certain people can't do it after 20. So that was my comment.

DR. TALAMINI: I'm sure this is a bridge too far, but our surgery residents now are videotaped as part of their training.

Dr. Fennal.

DR. FENNAL: Yes. I wasn't hearing very well, but I believe that it's appropriate now if I can make a comment on the labeling of the age range. Are we there?

DR. TALAMINI: Yes, ma'am.

DR. FENNAL: I would like to ask if maybe consideration of the age range saying 18 and above, that's okay. But I need to remind everyone that nowadays 18 to 26 is adolescence. Adolescent females do not make decisions like adult females. And so I think

that there may be some less responsible decision making on that if you are an adolescent versus if you are an adult female. So maybe just considering that.

DR. TALAMINI: Okay, thank you.

Okay, we've actually been a little bit over an hour. It's been a terrific discussion thus far, and I'm feeling the drive towards a break, but we should probably talk about the post-approval study proposal briefly, and then we'll take a break, and when we come back, we'll directly and formally address the questions. So thoughts about what you've seen in the post-approval study. We've already heard one specific -- I think from Dr. Iglesia. You just mentioned something that's escaped my memory.

DR. IGLESIA: No, I was talking about the registry and how we can monitor outcomes by surgeon, by patient type.

DR. TALAMINI: So I don't recall in the proposed post-approval study whether it included specifically a registry or not. But would you like to address that, Sponsors, please?

MR. BELOW: Paul Below.

That's correct. Our proposal to FDA did not include a registry at this time.

DR. TALAMINI: So what do other Panel members feel about that, about the proposal for a registry in a post-approval study?

Yeah, Dr. Inge.

DR. INGE: Tom Inge, Cincinnati.

I don't know exactly what we're talking about in terms of a registry, and I don't know if everybody has the same conceptions about it, but I would be proposing in favor of a well-matched, prospective cohort that is not getting the procedure, at the very least, to give us

estimates of things that we don't know yet. We don't know what the expected incidence of new organ extrusion is -- not extrusion, but --

UNIDENTIFIED SPEAKER: Erosion.

DR. INGE: Yes. Nor pain. So I think that these kinds of low-frequency -- you know, admittedly low-frequency adverse events and even maybe some higher-frequency adverse events that we haven't discovered yet, we'd benefit from that rather than some other population that may have its own limitations.

DR. TALAMINI: So the trick is we need to make a decision and a vote individually based on the data that we have. If the vote were no, one could recommend that that sort of a study might help in a separate approval application, I suppose. But then a separate issue would be if the FDA does approve this, depending on our recommendation or not, what kind of data would you like to see after it's approved?

DR. INGE: I was talking about after.

DR. TALAMINI: After.

DR. INGE: I was talking about after.

DR. TALAMINI: So you would actually propose a matched trial as a post-approval study?

DR. INGE: A comparison group that is not undergoing the surgery in the post-approval.

DR. TALAMINI: Dr. Fisher, is there protocol for that? Has that been done previously?

DR. FISHER: I'm not sure, but I was also going to ask could there be other -- I mean,

would you allow other medical interventions? How long would you follow it out? Thoughts?

DR. INGE: I think that if most of the events are happening in this, or the events that we're worried about today are happening, you know, in a mean follow-up time of 40 months, you know, everyone's beyond 2 and most people are beyond 3, I would say that you'd pick up, you know, the important things in that time frame.

DR. TALAMINI: Dr. Hicks.

DR. HICKS: Dr. Fisher, if you did a registry, can it be labeled as quality assurance? Is it going to be a medical/legal issue for the surgical community or not? I mean, if you do that, can people just gain access to it for nefarious reasons?

DR. FISHER: So we have a postmarket group who specializes in putting together registries, and if it's being suggested that a registry should be considered, I will take that recommendation back and see what we could do.

DR. HICKS: Okay.

DR. TALAMINI: So, you know, when we cover this again as a specific, we'll get everybody to say whether they think a registry should be included in a post-approval. But is there anybody on the Panel that would speak against some sort of post-approval study, if this were approved by the FDA?

(No response.)

DR. TALAMINI: No, okay. And we've heard the one modification that the Panel has brought forward for a registry. Any other thoughts on modifications for us to mull over ahead of and in anticipation of answering this question?

Yeah, Dr. Connor.

DR. CONNOR: Jason Connor.

So I would just reiterate that I would study, and I would leave it up to the Sponsor and FDA to figure out how, but just this role of stretching, because it seemed like stretching had far more to do with post-op pain than the type of surgeon potentially. So, you know, I could see the Sponsor may want everyone to do that just because it decreases pain and would look before for them, but to formalize the role of stretching, I think, would be valuable to understand if that's a real thing or a spurious finding.

DR. TALAMINI: Dr. Efron.

DR. EFRON: Yeah, Jon Efron.

The other thing that I would add is -- I'm sorry, I can't recall whether there is a standardized procedure for following up the mesh for possible erosion and whether it's visualization or palpation or some sort of standardized time frame over a period of time to evaluate erosion.

DR. TALAMINI: And Dr. Iglesia made a case for imaging.

DR. IGLESIA: Somewhat, yes. Perineal ultrasound, I think, will probably be the most -- the cheapest one by giving the most bang for your buck.

DR. TALAMINI: This post-approval study is getting more expensive by the moment.

(Laughter.)

DR. TALAMINI: Dr. Inge.

DR. INGE: I have a question for the Sponsor, I guess. One deviation from the current study that has been proposed, I guess, in the post-approval, is there a study entry criterion

of any condition that may compromise the outcome of the TOPAS system procedure as determined by the investigator? Which sounds to me like a great big, you know, insertion of bias for no reason. Why have that? Why have the investigator that may have a certain profile of a patient that's not going to do well, you know, with this out or with this condition that's inserted that wasn't in the premarket approval?

MR. BELOW: Okay. So these were draft criteria that we put together and used as a beginning discussion point with the Agency. Your point is well taken. Certainly, the exclusion of that particular criteria is something that we will consider. We look forward to working with the FDA after this meeting to craft the inclusion/exclusion criteria so the study meet its aims.

DR. INGE: Yeah. And don't get me wrong. If the investigators do have this sixth sense of something that is meaningful, then I think it should just be stated objectively as an inclusion or in the consideration for study entry criteria.

MR. BELOW: Thank you. Point well taken.

DR. TALAMINI: Dr. Afifi.

DR. AFIFI: Abdelmonem Afifi.

I have a question actually about the stretching and how it's done. It wasn't clear from the description that I read in the material. It said something like pull a leg to the chest and then roll sideways. Is it one leg at a time or both legs at the same time?

MR. BELOW: Thank you. Paul Below.

I'd like to invite Dr. Nihira to the lectern to describe. I would like to add, before he comes up, though, that when we looked at -- when we talked to the two urogynecology

centers that appeared to have lower rates of pelvic pain, this was one of the things that they told us. We didn't do a definitive analysis, and we can't answer the question that Dr. Fisher asked before that. We don't know if the others did or didn't do it. This was speculative. But we think that it deserves some further evaluation, but I will have Dr. Nihira come to the lectern to discuss how the stretching occurred at these two centers.

DR. NIHIRA: So the short answer is I don't know what they were doing. It has been proposed that before doing a transobturator procedure, that stretching and abducting one's thighs and selecting for that -- I select against patients who can't abduct their thighs beyond 120 degrees, but that is -- this is all very individualized stuff. So there is nothing standardized that I'm aware of.

DR. TALAMINI: Well, I would propose that we take a brief break, but let me ask the Panel members if there are any other questions in the front of your mind that you would like to address either to the Sponsors or the FDA, because when we come back, we will begin specifically answering these questions. And during that time it's just us. So any questions at the front of your minds before we take a break and take on that task?

(No response.)

DR. TALAMINI: No? Okay. Let's take a 15-minute break. I've got 2:52. So we'll come back in exactly 15 minutes. Thanks.

(Off the record at 2:52 p.m.)

(On the record at 3:08 p.m.)

DR. TALAMINI: At this time we'll call the meeting back to order, and we will focus our discussion on the specific FDA questions. Panel members, copies of the questions are in

your folders, and I would add that -- page 2, is it? Right, there's one sort of extra page that's missing. You've got 1 and then 2 is on the back, but there's a page in between those two that's a separate -- in a separate thing that you've got. If you have any questions about it, raise your hand and we'll get it figured out.

I would ask that each Panel member identify him or herself each time he or she speaks to facilitate transcription. So what we're going to do is we'll read these questions, and we'll ask each Panel member what your response or opinion is. You don't necessarily have to give exactly the detail that somebody else gave if you're of exactly the same opinion, but we do want to hear from every Panel member. If you don't have an opinion on that question, you can pass, and that's okay. And then after we go through what the Panel has to say for each question, it's my job to attempt to summarize that in a set of phrases for Dr. Fisher. So we'll go through these questions one by one.

Dr. Fisher, do you have any other comments for us before we begin?

DR. FISHER: No, good to go. Thank you.

DR. TALAMINI: Okay. So let us begin with Question 1. And I think we can cover all of Question 1 in one fell swoop.

MR. MARTIN: Timothy Martin with FDA Division of Reproductive, Gastro-Renal and Urological Devices.

DR. TALAMINI: Do me one favor, and for whatever reason, it's a little tough to hear up here. I think the sound is great in the rest of the room, but up here at the table it's a little tough to hear. So if you could speak right into that microphone, it would help all of us on the Panel.

MR. MARTIN: Panel Question 1: The primary effectiveness endpoint of the TRANSFORM study was based on subjects having at least 50% reduction in the number of fecal incontinence episodes documented by a 14-day bowel diary at 12 months compared to baseline (Responder$_{50}$ rate). The primary endpoint of the study was met based on the results of the first interim analysis of 80 subjects (52 out of 80 at 65%, with the probability p-value 0.0048). Among all 152 subjects implanted with the TOPAS System, 105 experienced treatment success, corresponding to a Responder$_{50}$ rate of 69.1% with a 95% confidence interval of 61.1% and 76.3%.

Please discuss whether these results support the effectiveness of the TOPAS device.

DR. TALAMINI: Thank you.

So let's begin with Dr. Kalota, and we will go around counterclockwise, to your right.

Dr. Kalota, do the results support the effectiveness of the TOPAS device?

DR. KALOTA: I believe it does.

DR. TALAMINI: Thank you.

And we've already had a rich discussion. So if you say yes and you have something to add to that discussion, please feel free to do so; otherwise, yes is fine.

Dr. Efron.

DR. EFRON: Jon Efron.

Yes.

DR. HICKS: Terry Hicks.

Yes.

DR. TALAMINI: Thanks.

Dr. Afifi.

DR. AFIFI: Afifi.

Yes.

DR. INGE: Tom Inge.

Yes.

DR. IGLESIA: Cheryl Iglesia.

Yes, for short term. And I'd like to see by-year outcome.

DR. CONNOR: Jason Connor.

Yes.

DR. DONATUCCI: Craig Donatucci.

Yes.

DR. FENNAL: Mildred Fennal.

Yes.

MS. BERNEY: Barbara Berney.

Yes.

DR. TALAMINI: So, Dr. Fisher, that one was rather straightforward. I think the answer to that is yes. And, of course, you've got lots of transcribed discussion points. Is that sufficient?

DR. FISHER: Yes. So thank you.

DR. TALAMINI: All right, let's go to Question 2, please.

MR. MARTIN: Timothy Martin with FDA.

Panel Question 2: The TRANSFORM study also had several descriptive secondary

effectiveness endpoints (Section 9.2 of Executive Summary), including the long-term effectiveness of the TOPAS Sling System, a reduction in incontinent days, a reduction in urge FI episodes, a reduction in symptom severity (the Wexner score), and other quality of life assessment tools.

Please discuss whether the results for these endpoints support the effectiveness of the TOPAS device.

DR. TALAMINI: Thank you.

This time, let's begin with Dr. Hicks, and we'll go the other direction.

DR. HICKS: Yes.

DR. EFRON: Jon Efron.

Yes.

DR. KALOTA: Susan Kalota.

Yes.

MS. BERNEY: Barbara Berney.

Yes.

DR. FENNAL: Mildred Fennal.

Yes.

DR. DONATUCCI: Craig Donatucci.

Yes.

DR. CONNOR: Jason Connor.

Yes, with a caveat that, for the primary, I think the 60-month is a benefit given this is a lifetime implant.

DR. IGLESIA: Agree, yes.

Cheryl Iglesia.

DR. INGE: Tom Inge.

Yes.

DR. AFIFI: Afifi.

Yes.

DR. TALAMINI: Okay. So, Dr. Fisher, again, with the background of the previous discussion, the Panel members feel that the endpoints are appropriate and do support the effectiveness of the device. Can we help you further with that, Dr. Fisher?

DR. FISHER: No, that's great. Thank you.

DR. AFIFI: Excuse me, Dr. --

DR. TALAMINI: Yes, Dr. Afifi?

DR. AFIFI: Before we go to the effectiveness, I wonder -- I had to ask for an analysis of the Sponsor that correlated 2 by 2 table. Is it appropriate to ask if they have done that analysis now?

DR. TALAMINI: Sponsors, can you respond to that for us before we move to safety?

MR. BELOW: Paul Below.

Yes, we can. So we did a 2 by 2 table. We looked at patients that had reported having pelvic pain at baseline as part of their medical history. And it's important to note that that data is -- that data was collected by patient interview. It wasn't done by a standardized exam. We then also looked to see, at their last available follow-up visit, if they reported a pelvic pain adverse event. So we've done the 2 by 2 table, and the results are

listed here.

DR. TALAMINI: Thank you. Perhaps you could leave that up during our going around.

Panel members, any further questions about that table, or do our statisticians want to opine before we address this question?

Dr. Connor? Dr. Afifi?

DR. AFIFI: Yes, I would like to make a comment. So among the patients who have had pain free, 24 continued to have pain and 60 did not. Among the patients who didn't have pain free, 19 had pain and 49 did not. In terms of a statistical test of this, we would compare the two at the upper right and lower left corners, ignore the other two. So we would then be comparing the 60 versus the 19. And I'm willing to perform the statistical test. It will take me about 1 minute. Would you like me to do that?

DR. TALAMINI: Please do.

DR. AFIFI: Okay.

DR. TALAMINI: If Dr. Connor hasn't already nailed it.

DR. CONNOR: Yeah. So McNamara's test has a p-value as 0.6 times 10^{-6}, if you're doing a McNamara's test?

DR. AFIFI: Yes.

DR. CONNOR: Yeah.

DR. AFIFI: Okay.

DR. CONNOR: And I input them right, yeah. So yeah, I mean, it seems like patients are three times as likely, if I'm reading this right, three times as likely to have pain go away

as to develop, right? I'm comparing the 60 to the 19.

DR. AFIFI: That's correct, yes.

DR. CONNOR: Yeah.

DR. AFIFI: I agree with that interpretation, yeah. Um-hum. So this, to me, is very convincing evidence that there is a beneficial effect to the procedure in terms of pain.

DR. TALAMINI: Thank you, that's very helpful.

So let's move on with that to -- that's the magic of statistics, gentlemen.

(Laughter.)

DR. FISHER: Before we move on, I'd like to thank the Panel.

DR. TALAMINI: So let's move on to Question 3.

MR. MARTIN: Timothy Martin, FDA.

Panel Question No. 3: The primary evidence provided in support of safety showed that there were 115 treatment-related (device and/or procedure) adverse events reported in 72 (47.4%) subjects. These adverse events included pain (43.5%, 50 out of 115), infection (21.7%, 25 out of 115), de novo and worsening pelvic organ prolapse (11.3%, 13 out of 115), and urinary problems (6.9%, 8 out of 115).

a. Please discuss whether the pain, which was the most frequently reported complication, has been adequately characterized and evaluated, and possible reasons for the pain.

DR. TALAMINI: So I think we'll have to go through each of these separately, but it shouldn't take too much time. So with respect to pain, discuss whether the pain, which was the most frequently reported complication, has been adequately characterized and possible

reasons for the pain. Again, we've already had a robust discussion.

Dr. Iglesia, would you like to begin? And we'll go clockwise.

DR. IGLESIA: You know, I think that that piece of -- that 2 by 2 table would've been nice to have seen, you know, earlier on. But to me, I think characterizing it by location and the fact that most of the pain, when present, was not severe, I feel like this has been adequately characterized.

DR. TALAMINI: Okay. Dr. Inge.

DR. INGE: I agree, I think it's been adequately characterized.

DR. TALAMINI: Dr. Hicks. Sorry, Dr. Afifi.

DR. AFIFI: Yes, I think that analysis that we have just talked about, that has convinced me that yes, there is a benefit to the procedure in terms of pain.

DR. TALAMINI: Dr. Hicks.

DR. HICKS: Yes.

DR. TALAMINI: Dr. Efron.

DR. EFRON: Jon Efron.

I think it's been adequately characterized. I'm not sure we have reasons for the pain, since there are two parts to the question.

DR. TALAMINI: Yeah. Fair enough, Dr. Hicks.

DR. HICKS: She -- Iglesia, we went through a big discussion of the possibilities. We couldn't isolate it, but we did the rainbow, the panorama of what it could be.

DR. TALAMINI: Indeed.

DR. IGLESIA: Right, I even said that I think that there's always going to be a baseline

level of pain, which probably is 2 to 5%.

DR. TALAMINI: Dr. Kalota.

DR. KALOTA: I believe it's been adequately characterized.

DR. TALAMINI: Okay. Ms. Berney.

MS. BERNEY: I would agree.

DR. TALAMINI: Dr. Fennal.

DR. FENNAL: Yes.

DR. TALAMINI: Dr. Donatucci.

DR. DONATUCCI: Yes.

DR. TALAMINI: Dr. Connor.

DR. CONNOR: Yes.

DR. TALAMINI: Okay. So let's do the same for (b), the rate of pelvic prolapse, which frequently required surgical intervention, and its potential association with the procedure, with the obvious other side of that versus being part of the disease.

Dr. Donatucci, maybe I could ask you to begin, and we'll go the other direction.

DR. DONATUCCI: Well, I must admit, even having listened to the discussion, I don't have a whole lot to add here, so I pass.

DR. TALAMINI: Do you think it's been adequately addressed?

DR. DONATUCCI: Yes, I do. And I can't contribute anything further. So I'm saying yes.

DR. TALAMINI: Okay. Dr. Fennal.

DR. FENNAL: Yes, it was adequately addressed.

DR. TALAMINI: Okay. Ms. Berney.

MS. BERNEY: Yes, it was adequately addressed.

DR. TALAMINI: Dr. Kalota.

DR. KALOTA: Yes, it's been adequately addressed.

DR. TALAMINI: Dr. Efron.

DR. EFRON: Yes, adequately addressed.

DR. TALAMINI: Dr. Hicks.

DR. HICKS: Yes, adequately addressed.

DR. TALAMINI: Dr. Afifi.

DR. AFIFI: Yes.

DR. TALAMINI: Dr. Inge.

DR. INGE: Tom Inge.

Adequately addressed.

DR. TALAMINI: Dr. Iglesia.

DR. IGLESIA: Yes, I agree. However, I think, remember this was a very well-selected population. No one had prolapse beyond 1 cm from the hymen, excluded Stage III and IV. And moving forward, I just would like to see what happens if this prolapse develops and people have this thing in place. Is that going to lead to obstructive defecation? That would be an important thing, too. I don't think we really discussed that. And the POP-Q wasn't -- I don't believe it was like a standard thing. But, you know, moving forward, that would be kind of an important thing. We see that in incontinence procedures, that people can develop cystoceles afterwards and then start developing some voiding difficulty. I'm just

wondering if it would happen if one were to develop an enterocele posterior compartment -- more posterior compartment prolapse with this thing, with the fecal thing in place.

DR. TALAMINI: Dr. Connor.

DR. CONNOR: Yes.

DR. TALAMINI: So, Dr. Fisher, with respect to prolapse, I think it's the Panel's opinion that the rate is appropriate for this population, the pathophysiology and its potential association with the procedure.

Okay, (c), Is the safety profile for this device for the intended population adequately described, as you've heard today?

Dr. Inge, could we start with you?

DR. INGE: I think that the safety profile has been adequately discussed today.

DR. TALAMINI: Okay. Dr. Afifi.

DR. AFIFI: I agree, it has.

DR. TALAMINI: Dr. Hicks.

DR. HICKS: This includes the discussions about labeling?

DR. TALAMINI: Not specifically. The labeling is a slightly -- that's a different -- well, let me ask Dr. Fisher. Maybe you could differentiate this specific Panel question versus the upcoming questions regarding labeling so the Panel's clear.

DR. FISHER: Well, I think for this question right here, we're asking a more broad question. Are there any outstanding issues regarding safety that we haven't taken into consideration? The labeling issue is going to deal more with what do we know and what needs to be put on the labeling.

DR. TALAMINI: So let's ask it that way. In the Panel's opinion, are there safety issues that have been missed in the studies in the discussion?

Dr. Iglesia's got some, but I guess we're going around the room.

So Dr. Hicks.

DR. HICKS: I would say, for the duration of the study, no. I mean, that it's correct for the duration, but that doesn't -- you can't look forward 10 years. I don't know what's going to happen. For now, I'd say yes.

DR. TALAMINI: Well, that's a legitimate statement, that the longer term has not been addressed obviously, and you've got concerns there.

Dr. Efron.

DR. EFRON: Jon Efron.

I would say that the safety concerns for the study time period have been addressed.

DR. TALAMINI: Okay. Dr. Kalota.

DR. KALOTA: I agree, yes, that we've discussed the appropriate safety issues for the time period that we're --

DR. TALAMINI: Okay. Ms. Berney.

MS. BERNEY: I would agree with the others, yes.

DR. TALAMINI: Dr. Fennal.

DR. FENNAL: Yes.

DR. TALAMINI: Dr. Donatucci.

DR. DONATUCCI: Yes.

DR. TALAMINI: Dr. Connor.

DR. CONNOR: Yeah, I agree with Dr. Hicks.

DR. TALAMINI: Dr. Iglesia.

DR. IGLESIA: Yes, for the most part. And this is, again, 150 patients, 1-year follow-up, well-characterized population and well-skilled surgeons who are fellowship or board certified trained in colorectal and urogynecology. And so this does not really safely address the generalizability nor the long-term safety of this mesh in this posterior compartment at 5 years.

DR. TALAMINI: So, Dr. Fisher, I think it's the Panel's opinion that the safety issues are adequately addressed within the confines of the study, but specific Panel members have concerns about the applicability more generally to both the broader surgical population, patient population, and over longer periods of time.

DR. FISHER: Yeah, thank you.

DR. TALAMINI: Okay, Question (d) in this one: Discuss whether the results demonstrate device safety for the intended population.

I think that's pretty much the same question. So I guess I would ask Dr. Fisher, do you want us to specifically address that in a differential manner? I think, as things have turned out, we pretty much addressed that in the last round of --

DR. FISHER: I believe we had. I think we're good to go.

DR. TALAMINI: Okay.

DR. AFIFI: I have a comment.

DR. TALAMINI: Dr. Afifi.

DR. AFIFI: I would like to go back to the question regarding racial and ethnic

composition of the sample that was looked at. This will probably come up in the post-approval study that we'll discuss, but I would have liked to have seen more data about Latino, Hispanic subjects, as well as more African-American subjects. But maybe this could be addressed in the post-approval study.

DR. TALAMINI: Thank you, Dr. Afifi.

Okay, next question.

MR. MARTIN: Panel Question 4: The applicant has proposed the following Indications for Use for the TOPAS System: "The TOPAS Treatment for Fecal Incontinence is intended to treat women with fecal incontinence (also referred to accidental bowel leakage) who have failed more conservative therapies."

The inclusion and exclusion criteria for the study required that subjects be 18 years old and over, not pregnant, and not planning a future pregnancy, and that subjects have failed two modalities of conservative therapies such as dietary modification, pharmacologic intervention, or pelvic floor muscle training.

a. Should the labeling exclude patients who are pregnant or may become pregnant?

DR. TALAMINI: I think we could do all three of these at once. Why don't you go ahead and read (a), (b), and (c), please?

MR. MARTIN: (b) Should the labeling include any age restrictions? (c) Should the labeling specify other interventions that should be used prior to the use of this device?

DR. TALAMINI: Perfect. So, Dr. Efron, perhaps you could address each of those, (a), (b), and (c).

DR. EFRON: Jon Efron.

So should the labeling exclude patients who are pregnant? Yes. Or may become pregnant? No. Should the labeling include any age restrictions? Other than above the age of 18, no. Should the labeling specify other interventions that should be used prior to the use of this device? No.

DR. TALAMINI: Dr. Kalota, you have similar ideas or add to that?

DR. KALOTA: Similar, I would say, for (c), should the labeling specify other interventions? Purely diet and noninvasive options.

DR. TALAMINI: So you would not mandate other attempted --

DR. KALOTA: Surgical.

DR. TALAMINI: -- therapies prior to the application of this device?

DR. KALOTA: Not beyond diet and -- I just lost the word that I want.

UNIDENTIFIED SPEAKER: Feedback?

DR. KALOTA: Yeah, biofeed or just --

UNIDENTIFIED SPEAKER: Pharmacologic.

DR. KALOTA: Yeah, pharmacologic and diet.

DR. TALAMINI: So what you're saying is you would be okay with this as an earlier line therapy than --

DR. KALOTA: Correct.

DR. TALAMINI: -- it is proposed?

Ms. Barney. Berney, sorry.

MS. BERNEY: I'm going to pass on this one.

DR. TALAMINI: Pardon?

MS. BERNEY: I'm going to pass on this one.

DR. TALAMINI: Okay, no problem.

Dr. Fennal.

DR. FENNAL: (a) Should the labeling exclude patients who are pregnant? Yes. Or may become pregnant? No, with good education and explanation. (b) Should the labeling include any age restrictions? Yes. Should the labeling specify other interventions that should be used prior to the use of this device? Yes.

DR. TALAMINI: Okay. Dr. Donatucci.

DR. DONATUCCI: I agree.

DR. TALAMINI: Dr. Connor.

DR. CONNOR: Yeah, I agree on (a) and (b), and I think I'm content with the label as proposed for (c).

DR. TALAMINI: So we've got a little difference of opinion going in terms of what intervention should be required prior to the application of this device. You would come down as proposed in the labeling, or would you liberalize and allow it to be used at an earlier stage?

DR. CONNOR: So Jason Connor.

I'm not sure I understand the difference between the proposed label and what Dr. Kalota was saying, because she was saying dietary, pharmacologic, and it adds pelvic floor muscle training. But the label says two of those, which would include diet and pharmaceutical intervention.

DR. TALAMINI: Fair enough.

DR. CONNOR: So is it actually different?

DR. TALAMINI: Fair enough. Probably not, probably not.

DR. CONNOR: Okay.

DR. TALAMINI: Dr. Iglesia.

DR. IGLESIA: So, you know, I'm very conservative, and I would prefer that this not be used in people who are still wanting -- who are definitely not pregnant, but those who are wanting future fertility. I think that we should have longer-term data before we consider that. Secondly, that being said, if someone was like 18 and not planning any children and they get their tubes tied or a hysterectomy or something, I don't think there's any age restrictions. But can you go back to the slide before?

Because I think, for full disclosure for patients, you know, you write down two modalities: diet, Lomotil, pharmacological, or biofeedback. But we have other modalities that I think patients should be aware of, including the newest FDA-approved Eclipse device, which is a fecal incontinence pessary that you place into the vagina, and it basically occludes the rectum. And then, secondly, there's neuromodulation or Interstim. And I just think, for full disclosure, I think -- and unfairly, there is the overlapping anal sphincteroplasty. Probably this is superior to that, but we don't have any head-to-head data for me to actually say that. But just looking at what the long-term data is, I just feel like they should at least be made aware that there are other options, including nonsurgical with the Eclipse.

DR. TALAMINI: But in terms of those other options, you would agree with two of

them prior to the application of this?

DR. IGLESIA: This is not an all-inclusive list, right?

DR. TALAMINI: Okay, got it.

Dr. Fisher.

DR. IGLESIA: I'm not interpreting it to be that.

DR. TALAMINI: Dr. Fisher.

DR. FISHER: Excuse me. Fisher, FDA.

I just want to clarify here that the actual labeling is that small paragraph that's in italics right there. When we start talking about the inclusion/exterior -- excuse me, inclusion/exclusion criteria, that's not actually part of the labeling. So the one thing -- so for clarification, I guess -- you know, one thing that's on the table is for individuals who have failed conservative therapies or what I might be hearing, if we take everything into consideration, patients who have failed all other therapies. So I just want to get clarification on where you stand on that.

DR. IGLESIA: Yeah. I mean, there were several patients -- I think, if I remember correctly, and you can pull it up, 20% of your study -- of the 150 had had prior surgery, had had overlapping sphincteroplasty. And it wasn't a risk factor for failure, but clearly, you know, this was the last resort for those, in lieu of a colostomy.

DR. TALAMINI: Donatucci.

DR. DONATUCCI: Yeah, I just wanted to make a comment about -- I agree, all patients need informed consent. However, I disagree that the label is where alternatives to -- alternative surgical procedures or basic procedures should be listed because they change,

and I think that diet, exercise, pharmacologic therapy doesn't specify a specific therapy. It's just a less invasive form of therapy prior to moving on to invasion. So I would disagree with -- I don't have a problem with informed consent, as you discuss it, just not a specific list of procedures.

DR. INGE: Yeah. And especially if there hasn't been a head-to-head trial with these other devices. That puts an unfair burden on them to essentially promote potentially products that are not their own.

DR. TALAMINI: So can we go back to the (a), (b), (c) slide? And Dr. Inge, I think it's your turn on the (a), (b), (c).

DR. INGE: Yeah. A few things. I'm just thinking aloud here, but also with the microphone. Is there something missing? I mean, why is it that you guys put pregnancy there? Is there a risk to -- is there some risk here, a vulnerability of pushing a patient potentially toward C-section that you would say -- is that why you would come down and say no pregnancy and not to become pregnant?

DR. TALAMINI: Yeah, you can address.

MR. BELOW: Paul Below.

I'd like to invite Dr. Fenner to address that question.

DR. FENNER: Well, I think during pregnancy is obvious. I mean, you don't want to do an elective procedure during a pregnancy.

DR. INGE: Correct.

DR. FENNER: And especially in this area. No, I think it was just that because we just didn't know, and if a woman thought she was going to have future deliveries, it would make

it difficult to follow out. During this initial study, if she got pregnant, we would think that if it's working, we'd want her to have a C-section. So that was for the trial, in terms of that. And so I think, as I discussed earlier, you know, if she's happy and she's confident, I would make her have a C-section, and that would be with pretty much any other treatment I had for her fecal incontinence. I just wouldn't push it since so many of these women, the etiology is obstetric.

DR. INGE: Sure. So yes, I would agree with -- I guess it was Jonathon who first changed that, a notion that they should not -- they should be able to -- it's not to be used when they're pregnant, but not to say that they can't become pregnant. The age restrictions, I entirely agree with what has been said. I would only use this as an opportunity to say again, as a pediatric specialist, that we would like to see studies in the younger age groups that also stand to probably benefit from this. And the interventions, I think we've talked about. Conservative interventions, not necessarily other invasive interventions, need to be labeled.

DR. TALAMINI: Dr. Afifi.

DR. AFIFI: I would go along with what Dr. Kalota has said.

DR. TALAMINI: Dr. Hicks.

DR. HICKS: I have two questions. Can we go back to the other slide? Since we're putting in what -- those are considered conservative therapies. If you're going to put that in there, should you put other failed procedures? Should you put it in there? In other words, do you have to try these? What if I took Interstim and I didn't try any of this stuff? I mean, should you include everything? It's easy to stay out of a sentence and say or failed

procedures. You have to say what they are. I have unsuccessful procedures.

DR. TALAMINI: I would suggest that, by implication, it would be acceptable to use it after more invasive procedures had been attempted, just not as the very first therapy.

DR. HICKS: Well, then I guess you'd have to go back and make sure, then, does that hold true, that they ought to go back and have to try? Somebody might take them right to an Interstim. Do they need to come back and do pharmacological and all of that?

DR. TALAMINI: Yeah.

DR. INGE: That's not how they did the study, though. They may be at more risk.

DR. TALAMINI: Yeah. It sounds like there may even be some wordsmithing.

DR. HICKS: No, here's the issue. The issue is this and the other issue, if we go to the next slide, is the question about the pregnancy issue. I mean, I don't know how you put -- unless you have a consultation with a physician skilled in this area is really the reality, and that's what you'd want for safety. I don't want you just talking to anybody. I don't want you to be talking to some gynecologist who doesn't understand any of this, somebody who does this before you get pregnant, you know? I mean, I guess maybe the person who's going to put it in is going to tell you that. I won't put it in if you're pregnant and all that. There's just some medical/legal issues, and there's also just the general, our responsibility to the public. What is it? What do you think, Mark?

DR. TALAMINI: Well, you know, it's each of our opinions. So, you know, in other words, what do you think? Should labeling exclude patients who are pregnant or may become pregnant?

DR. HICKS: At this point, we don't have any data to say that it's safe to do. We

don't. So if you pick by where we are right now, that's correct, wouldn't you say?

DR. TALAMINI: It should exclude patients.

DR. HICKS: Yes.

DR. TALAMINI: Okay.

DR. HICKS: Okay.

DR. TALAMINI: And should it include age restrictions?

DR. HICKS: From the data we have, yes.

DR. TALAMINI: Yeah. And any other interventions? It sounds like you'd call for a little wordsmithing there, but you believe in the principle.

DR. HICKS: Right.

DR. TALAMINI: Okay.

Dr. Faulx, out of sight, out of mind. My humble apologies. What's your vote?

DR. FAULX: I was texting my vote, then. Yeah, I didn't have any further thoughts on that. I think that it's reasonable to exclude pregnant patients and, I think, may become pregnant. And I think as the surgeons, the gynecological surgeons, were saying, you know, they themselves -- C-sections. And would recommend all the patients who are having these troubles to have C-sections. No other labeling restrictions besides over 18. And I thought the labeling seemed reasonable.

DR. TALAMINI: Okay, terrific.

So, Dr. Fisher, in general, after some discussion, I think that the Panel indeed thinks that labeling should exclude patients who are pregnant. Becoming pregnant is a little more controversial, and it sounds like some would vote for the labeling to at least include a

warning in that regard. It should include age restrictions. And (c) might need a little wordsmithing to be clearer. Does that get at the points for you, Dr. Fisher?

DR. FISHER: Yes, thank you.

DR. TALAMINI: Okay, Question No. 5.

MR. MARTIN: Panel Question 5: Labeling. In the clinical study, urogynecologists and colorectal surgeons implanted this device. There was no statistical difference shown for the primary effectiveness endpoint; however, regarding safety, there was a trend toward fewer AEs (for example, pelvic pain reports, pain duration, pain resolution) following implantation by urogynecologists. Please discuss the following:

a. the clinical training or experience that should be required for physicians implanting this device;

b. other measures that could be taken to ensure patient success.

DR. TALAMINI: So I think our best approach, given the discussion that we've had to this question, is to use what's been presented to us by the Sponsors, as their clinical training paradigm is the baseline, and state whether we think more should be done or whether that's adequate or less needs to be done and what other measures you would add in terms of ensuring patient success.

Dr. Faulx, could I prevail upon you to start this one?

DR. FAULX: Sure. So I think what was pointed out in the differences maybe had to do with stretching. So I certainly think, you know, going back to those with the low rates of pelvic pain and trying to figure out what that regimen might be, to maybe include that in the training for the various centers just to see if that, you know, may decrease the amount

of pain these patients had. But, again, I think the training program sounds great. I just think that everyone's going away from numbers sort of universally, and so some way to assess competence when someone comes and does this training and maybe have some sort of test that they can do or, like you were saying, videotaping or something versus just coming up with the discrete numbers, that they meet certain competencies with doing this before they can do it on their own.

DR. TALAMINI: Other measures?

(No response.)

DR. TALAMINI: No? Dr. Connor, do you want to take this up? And then we'll go clockwise.

DR. CONNOR: I know nothing about training surgeons, so I don't know if I can speak too much. I mean, in terms of the difference, I'd reiterate that I think if you did a multivariate model of specialty plus the stretching program, it completely goes away, and all the action is in the stretching program, though we understand little about it and how compliant patients were. So I think that's something for the post-approval study. But I don't think I would make any changes to the label based upon these two questions. But I don't know enough to answer that very well.

DR. TALAMINI: Dr. Iglesia.

DR. IGLESIA: Cheryl Iglesia.

So, you know, for the most part, I actually really do appreciate the model because I think that it's much more robust to have those modules, to have the simulation and/or cadaveric actual dissection things. And the thing, the little simulator that was developed at

Oklahoma was kind of cool. And the second thing, however, is the preceptoring intraoperatively. However, I'd like to go a little further and having postmarket surveillance on all of these surgeons every time they're putting in, whether it be their first -- I don't know.

However, we are marketing with patient-centered outcomes and surgical -- any kind of serious adverse events to see if there are trends because, as I said, it may take more than two, you know, for people to actually do this right. And I think if there are signals, it should be noted earlier. In terms of other measures that should ensure patient success, well, it looks like the stretching exercises may be useful. And so I'd like to see more analysis on that.

And, secondly, I think that with that 69%, it was pretty good, but what about those 31% of women who didn't get the R_{50}? So what is it about those patients? I'd like to be able to have more robust studies to try and figure that out, whether it be preoperative imaging or nerve testing or more of the manometry or pelvic flood muscle strength at baseline, something. Because I think that we need to, as we develop this algorithm, kind of be able to guide patients into, you know, things that we think are going to be helpful for them. That's going to take some time. But I'm a big advocate of the registry for this, for postmarket surveillance.

DR. TALAMINI: But what do you think should be on the label in terms of clinical training and other potential --

DR. IGLESIA: Oh, okay. Yeah. So yeah, you should be like either board certified or board eligible in colorectal surgery or female pelvic medicine and reconstructive surgery,

which could either be OB/GYN or female urology based, by the way. And, secondly, you have to have gone through those models and passed the tests or whatever needs to be done. You have to have been proctored. And obviously I would like to be able to submit your cases to the registry.

And, you know, you had a question, Dr. Inge, like you wanted prospective comparative studies. So that can be done because you could do that within a nested cohort within a registry. So you can see multicenter, you know, patients who are undergoing, I don't know, say that pessary thing, which can be also looked at on this new device. Or say, you know, patients who are undergoing the direct sacral stimulation, if you wanted to look at it head to head. But that kind of information would be very helpful in the future for counseling.

DR. TALAMINI: Post-approval study, though, right?

DR. IGLESIA: That would definitely be post-approval.

DR. TALAMINI: Okay. Dr. Inge, what should go on the label?

DR. INGE: I have no doubt that Dr. Fisher's expert team in post-approval can help with the details of that design and, to your point, make it a useful valuable study to know what the natural history or the expected incidence is of these problems.

DR. TALAMINI: That's next, though. You get to talk about that next.

DR. INGE: The label, it's tough. And I don't know that I agree with the notion of restricting the trade of general surgeons who are expert at pelvic surgery just because they don't come with colorectal credentials or they don't come with gynecologic credentials. So I wouldn't necessarily deviate from exactly what has been done. People are very different

in their skill set that they come into new operations with. And so it's, I think, better to leave well enough alone with that.

Other measures. I would just say, even though there was not statistical significance to this trend or this exploratory analysis demonstrating that patient preparation in the form of exercise may have been associated with better outcomes, at least vis-à-vis lower pain scores, I think it's inherent upon all of us who look at the results of improvement science now and look in particular at the early recovery after surgery data and find that patient preparation before surgery is incredibly important to seeing best outcomes. So I would just say that that would be a strong advice is if you have -- kind of play the winner. If you have best practice centers, what they're doing that seems to make sense in terms of patient preparation, then make that part of the algorithm.

DR. TALAMINI: Dr. Afifi.

DR. AFIFI: The only comment I have is about the stretching exercises, but I think maybe the first thing we should do is to know what they are.

DR. TALAMINI: Dr. Hicks.

DR. HICKS: I'm going to need some help. The things that seem to be appropriate, one is, I don't know what the verbiage would be, adequate pelvic surgical experience, and that way that could include general surgeons who've done adequate pelvic surgical experience. Participation. I don't know how you want to call it, the course that they would provide with a cadaver and everything. Is the company going to provide that? They said you got to go and take that, much like other companies have done.

DR. TALAMINI: So I don't think we would need to necessarily say who would do it,

but we could use what they've done and say --

DR. HICKS: Right.

DR. TALAMINI: -- that's a good benchmark.

DR. HICKS: Participation in a cadaveric whatever. And then the -- I don't know how you put it either, for somebody to sign you off for preceptorship. It's more than just taking a preceptorship and having them sign off essentially, and I don't know what the sweetest verbiage on that would be. Just because you came and watched and I think you did three really poorly, you know --

DR. TALAMINI: A proctor. It's a proctor, usually.

DR. HICKS: Proctor. Yeah, but it needs to be somebody to sign off on it. It's not just to be able to go watch a course and get -- and go back and do that. So I think the proctor should -- in some form you get a form saying that you adequately passed the preceptorship or whatever it's going to be.

DR. TALAMINI: Dr. Efron.

DR. EFRON: I would say that I don't have anything different to add, except that I agree with the way the clinical study requirements were set up, and that would be adequate for labeling. And, again, others mentioned preconditioning techniques that may reduce pain.

DR. TALAMINI: Dr. Kalota.

DR. KALOTA: I like the labeling now, and I like the idea that they're looking to identify practitioners who have specialty in pelvic floor. But my question is, if the labeling now says your gynecologists and colorectal surgeons, is that forever, or does that get

looked at later? If this becomes more commonly performed surgery and you're learning it in your residency, does that mean if you don't specialize, you never have the opportunity to do it? So is this looked at again in the future? If we label it as such now, is that forever? Or can we, like Dr. Hicks said, someone who's proficient in pelvic floor peritoneal surgery be --

DR. TALAMINI: Dr. Fisher.

DR. FISHER: Okay. So we gave you guys kind of a trick question, okay, because when it comes to the labeling, we have to be very, very careful as to specifically -- we cannot specifically require a certain discipline of medicine to do something. So it would go down as something more general where somebody who's knowledgeable, you know, with procedures. And when it comes to training, we can require training, but we can't really dictate what goes into that training. So your comments are very valuable to the Sponsor right now for their training program because we will have an opportunity to review and provide input on their training program. So I know that they're taking notes over there, also.

DR. IGLESIA: I have a question for Dr. Fisher, though. So if somebody was trained and they've gotten their proctorship and they're doing this, however, for two things, they do fewer than eight a year or they have really bad outcomes, if we end up doing some kind of surveillance, then I think that has to be kind of accounted for, when the Sponsor, like, oh, that person's privileges or need some extra training.

DR. TALAMINI: The problem is that's a hospital credentialing issue.

DR. FISHER: Thank you. Yeah.

DR. TALAMINI: But hospital credentialing committees pay great attention to

societies' input, industry input, FDA input. But ultimately it comes down to what privileges you have in your local hospital.

Did you wish to make a comment?

MR. BELOW: We do, thank you. Paul Below.

I'd like to call Ryan Casey to the lectern to address our company perspective on this issue.

MR. CASEY: Thank you. Good afternoon. My name is Ryan Casey, and I am the senior manager of global education and training for ASTORA. Yes, we have -- we are taking into account the quality of physician that -- the surgical quality of the physician that we want to have access to this product. So when we are looking at our training program, we are looking at -- as we did with the study, looking for FPMRS and board-certified urogynecologists and colorectal surgeons at this point that have -- that are currently treating FI patients and that have experience with surgical mesh or other surgical implantations for fecal incontinence. We're putting that in place for ourselves. And when we do look at the proctorship, we are going to put in place not only in the proctorship but at the training courses the cadaver labs, a faculty assessment of the participants, that they're able to successfully follow the procedural steps for implantation of this device. And that will also be included in the proctorship. So it will be -- again, we are not credentialing the physician on their surgical expertise, but we are -- we will be able to observe and assess their ability to correctly implant this device.

DR. TALAMINI: Thank you.

Okay, I need to get us back on focus here. So we're in mid-question, and we are

around to Ms. Berney, and the question is as on the screen here, in terms of labeling for training and other measures.

MS. BERNEY: I think just about everything that needs to be said has already been said. I can't add anything.

DR. TALAMINI: Thank you.

Dr. Fennal.

DR. FENNAL: I defer to the urogynecologists.

DR. TALAMINI: Dr. Donatucci.

DR. DONATUCCI: I have nothing further to add. I have nothing further to add at this point.

DR. TALAMINI: Thank you.

So, Dr. Fisher, a little bit less clear on that one. But, in general, I believe the Panel agrees that there should be a training program and that the examples they've seen today appear effective with perhaps some tweaking, and there's lots of thinking about additional data. And down the road, it really spills over into what would be a post-approval study, it sounds like. Does that address the need?

DR. FISHER: It sounds like we've already started to kick off the post-approval study conversation.

DR. TALAMINI: Indeed, thanks.

Dr. Faulx, any further comments?

(No response.)

DR. TALAMINI: Lost her. Next question.

MR. MARTIN: Timothy Martin, FDA.

Post-approval study. Note: The inclusion of a Post-Approval Study section in this summary should not be interpreted to mean that FDA has made a decision or is making a recommendation on the approvability of this PMA device. The presence of a post-approval study plan or commitment does not in any way alter the requirements for premarket approval and a recommendation from the Panel on whether the risks outweigh the benefits. The premarket data must reach the threshold for providing reasonable assurance of safety and effectiveness before the device can be found approvable, and any post-approval study could be considered. The issues noted below are FDA's comments regarding potential post-approval studies, for the Panel to include in the deliberations, should FDA find the device approvable based upon the clinical premarket data.

The applicant is proposing to conduct two post-approval studies. The first proposal, the Extended Follow-up of the Premarket Cohort, is a continuation of the premarket study cohort; the second proposal is a New Enrollment post-approval study that will enroll patients in the U.S. and Europe. The overall goal of these PASs is to evaluate the long-term safety of the TOPAS system in the postmarket setting in women with FI who have failed more conservative therapies.

Panel Question 6: For the two proposed post-approval studies, the primary safety objective is to demonstrate that the proportion of subjects experiencing at least one device- and/or procedure-related serious adverse event meets a performance goal.

- For the Extended Follow-up of the Premarket Cohort, the proposed performance goal is 25% at 60 months.

- For the New Enrollment post-approval study, the proposed performance goal is 20% at 36 months.

These performance goals are based on the performance of a different device that does not modify the anatomical structure of the pelvic muscles (Interstim sacral nerve stimulation therapy). FDA is concerned that these performance goals are too high. The FDA recommends the applicant take into consideration the nature of the implanted device, the risk-benefit ratio, and the results from the TOPAS premarket study when developing the performance goal for the post-approval study.

Please discuss the appropriateness of the 25% and 20% performance goals listed above.

DR. TALAMINI: So this we didn't discuss in as much depth in our Panel deliberations. So perhaps, Dr. Fisher or the FDA, you can help us read between the lines of this question a little bit and fill it out to enable our answering this question.

DR. FISHER: Sure. So the Sponsor has put forth a performance goal, and the performance goal is based on the performance of a sacral nerve stimulator, which has recently been approved, and there are some basic fundamental differences between these two devices. One you can take out, and you can change the settings on it. The other one is a permanent implant. So the question that we're asking the Panel is that, right now, the Sponsor has suggested that a 25% AE rate is acceptable at 60 months, and for the second study, 20% is acceptable for the 3 years of the second post-approval study. And the question is, do you think it's appropriate to set a performance goal on another device which operates through a different mechanism, or it might be okay, and if you think those

numbers are -- do you think 25% is acceptable? Too high, too low?

DR. TALAMINI: Dr. Afifi, your initial thoughts.

DR. AFIFI: Yeah, my first thought is if the FDA thinks that these may be too high, relative to what? Really, I mean, what have you looked at that made you think, well, maybe this is too high a bar line?

DR. FISHER: Fisher, FDA.

Once again, these numbers are based -- come largely from what we see with the other device. So that's where they're getting their numbers from. So the question is, do the differences in technology between the two devices justify those numbers?

DR. AFIFI: Okay. Then you do have -- in other words, you have data that show that maybe a little lower percentage is more reasonable, in which case I would definitely go along with that. But I don't know what those data are. So, you know, I serve on some data monitoring committees and so on, and as you know, this question always comes up, and there really are not standards, as such. So it's a gut call based on some, I guess, experience. And in this case, maybe the experience shows that let's lower this a bit. And I don't know if I could say any more than that.

DR. TALAMINI: Can you further enlighten us? I think the struggle is, you know, what's the reference point for these numbers, and how can we assess, from where we sit today, whether they're too high or too low? A little tough.

DR. BAYONA: I don't know if I can have my -- the backup slides so I can show you the information that I have here.

DR. TALAMINI: Dr. Hicks, do you have a specific question?

DR. HICKS: Yeah. Before you go, maybe, Dr. Fisher, define what the performance goal really is. It's not really clear. I mean, is it that you reached adequacy, that it was safe or not? I'm not sure exactly how to define what it is.

DR. FISHER: Okay. So a performance goal is basically a target that you try to hit. It is different than an objective performance criteria, which is one that is actually based on a statistical analysis of data, okay? So a performance goal can be obtained in a variety of different ways, and sometimes you don't know what the target is that you're setting. So sometimes you don't have data.

DR. HICKS: You give this example and they want to do 20% --

DR. FISHER: Hang on, hang on.

DR. HICKS: I'm sorry. Say the goal is 20%. Twenty percent of what? Since you can measure it so many different ways, what are we -- it's not clear.

DR. FISHER: Well, in this one, I believe it has to do with --

DR. TALAMINI: Serious --

DR. FISHER: -- serious adverse events, which are defined.

DR. TALAMINI: Yeah, serious. A single serious adverse event. So it's 25% having a single serious adverse event.

DR. FISHER: Twenty-five percent of the patients having a serious adverse event at the end of the study. So the first one is carrying out to -- so it would be 25%, 25% of the patients at 5 years.

DR. HICKS: Or less. Is that it?

DR. FISHER: Correct.

DR. HICKS: Twenty-five percent or less.

DR. FISHER: So if it goes above that -- yeah, sorry.

DR. INGE: The PMA is at 5% at 3 years, right? The PMA is showing us 5% at 3 years. That's what the disconnect is for me.

DR. TALAMINI: Dr. Connor.

DR. CONNOR: Yeah. And I think I can shed some light on this because I reverse-engineered what numbers they need to meet that.

DR. FISHER: Thank you.

DR. CONNOR: So the 25% at 60 months. So that's based upon following the current -- 70 patients of the current cohort onward. So to meet 25%, it's sort of an upper bound for the confidence interval, which is what they mean they would have to observe 16% or less. So they have to have an observed rate of 16% or less to meet this 25% goal. For the new patients, which is the 20% -- that's what's on the screen here -- and it's lower because it's 36 months. Obviously, the longer we track people, the more of these older patients with comorbidities, you're going to have events. This is an 88-patient study they're proposing, and they would have to observe 13% or less to meet -- statistically be better than 20%. So does that help shed some light on what this means? So 13% or less of 88 new patients would have to have SAEs before 36 months to meet this goal.

DR. TALAMINI: And if I understand, the FDA is saying they believe that's going to be a difficult bar to meet because it's based on data from a different device; is that right?

DR. BAYONA: Well --

DR. FISHER: Go ahead.

DR. BAYONA: Yes. No, no. What we believe is that 20% is too high of a performance goal because we have seen that the other devices, and even this device on premarket has a much lower rate. So we don't believe that it's necessary to have it that high. You know, it's not realistic to have it that high. This performance goal was found -- on the interesting PMA there was 13%, and then they put the 7% margin, as was explained. So we believe that something a little more realistic will be more acceptable. And the same thing with the 25% performance goal.

DR. TALAMINI: Are you willing to proffer a number that you think would be more realistic?

DR. BAYONA: Yes, I have some preliminary calculations on the backup slides.

DR. INGE: And while they're testing that, maybe you can offer what are the consequences of not meeting the performance goal versus the performance criterion?

DR. FISHER: You know, ultimately, if it's a post-approval study, then the device has been approved. So probably the major impact is going to be, you know, depending on the data, we may have to, I don 't know, take some action to put out a notification, or we may ask for a change in the labeling. But at that point it will be approved.

DR. INGE: But, again, in the definition, what is the difference between the goal and the criterion? Does it have more teeth?

DR. FISHER: Actually, it boils down to a statistical analysis, and I'm really not the person qualified to answer that.

DR. TALAMINI: Go ahead, sir.

DR. BAYONA: Yes, if I may. This table includes the impact of different performance

goal levels -- oh, I'm sorry. This table includes the impact of different performance goal levels and the sample size needed for the follow-up extension of the premarket study, post-approval study, assuming a 12% serious adverse event rate, 85% power on one-sided 5% Type I error rate. The last column represents the sample size needed at 6 months of follow-up.

The applicant estimates that at least 94 patients from the current cohort will complete the 60-month visit, and that is why the current performance goal will require 70 patients. The 24% performance, if we lower it a little bit to 24%, will require 78 patients; 23% will require 86 patients, and that is still doable. And then 32% is going to be out of range because it's going to require more than the 94 patients that the Sponsor is anticipating to have at the end of the 60-month follow-up. This is for the extension of the premarket cohort.

For the new enrollment study, okay, this table includes the impact of different performance goal levels on the sample size needed for the new enrollment post-approval study, assuming a 9% serious adverse event rate, 90% power and one-sided 5% Type I error rate, as the Sponsor is proposing. The last column represents the sample size needed after taking into consideration an 8% annual dropout rate for 36 months of follow-up, as the Sponsor is expecting. And we can see here that if we lower it from 20 to 18%, the sample size will increase to 162, 16% performance goal will be 249, and 15%, that we believe that will be more reasonable, will require 325 patients. That we don't think is an extremely large study.

DR. TALAMINI: So I'm going to guess that most of the Panel members don't feel

equipped to speak intelligently to this issue, just judging by the looks on people's faces. So what I might ask is if there are Panel members that do feel qualified or informed enough to speak to this question, and it might likely be our statisticians, please do so, because I think for the rest of us, it's probably a little tough to apply our clinical brains to this problem and come up with an effective response.

DR. FISHER: Did you have something, Jason?

DR. CONNOR: All right. Jason Connor.

So I think have two comments, one the Sponsor will like and one they won't. So regarding, you know, what was proposed, I think the key is, you know, an observed rate of 13% is still what it would take to "meet the level" of that first one, and 13% is actually what was observed in, you know, another trial of a less invasive device. So to achieve the goal -- and so the goal looks bad. It's 25%. But to actually meet it, they have to observe a 13% event rate or better, which is to say their event rate is, you know, equal to a less invasive device or even better, which is a pretty high bar and a challenge. And, in fact, to power that, they assume their event rate was even lower than Interstim. And people assume things that aren't true all the time, so their powers look good. So that may be what happened. So I think that that's actually relatively challenging. And in the slides, they showed for bigger sample sizes and lower bars. For instance, the 22% rate, which they would need 107 patients for, they could observe 15% and actually meet that. So it looks better. It's a 22% threshold instead of 25, but they could actually meet that with the higher observed event rate. So whether that's actually better, it looks better, but the observed event rate is higher. More so than, you know, kind of all the numbers and stuff like that.

The bigger challenge I have with these post-approval studies is that there's no incentive for sponsors to follow people, right? Like if they're lost to follow-up, they can't show us significant adverse events.

And having interacted with, you know, some other sponsors on these, I'm just -- you know, I question how well these patients are followed. They report something to their primary care physician, who has no idea the patient is in this trial. You know, is just diligent observation of the MAUDE database better than trying to follow 70 patients who we may not really keep track of all that well? So I think more so than any numbers we lay out, the idea of missing data and a sponsor's disincentive to actually follow patients is the bigger issue.

DR. TALAMINI: Dr. Afifi, further thoughts?

DR. AFIFI: No, not really. I have nothing to add.

DR. TALAMINI: So I'm not sure we can help you a lot more with this one, Dr. Fisher.

Dr. Hicks has a comment.

DR. HICKS: Unless Jason comes up with a plan.

DR. TALAMINI: To this.

DR. FISHER: So lesson learned. If there's a topic that should be really discussed during deliberations, it should be discussed during deliberations --

DR. TALAMINI: Yes.

DR. FISHER: -- and not wait until we vote on the questions.

DR. TALAMINI: Fair enough.

DR. FISHER: But point taken. Thank you very much.

DR. TALAMINI: So Question 7, however, we have discussed at some length. So let's go on to Question 7.

MR. MARTIN: Timothy Martin, FDA.

Post-approval study. Panel Question 7: Regarding the New Enrollment post-approval study:

a. Does the Panel have any recommendations about the method or schedule of diagnostic surveillance for following subjects in relation to pain?
b. Does the Panel have any recommendations about the method or schedule of diagnostic surveillance for following subjects in relation to pelvic organ prolapse?
c. Does the Panel have any recommendations about the method or schedule of diagnostic surveillance for following subjects in relation to other adverse events?
d. Are there any other concerns which the Panel recommends the post-approval study address?

DR. TALAMINI: So I think in approaching this in our deliberations, the Panel had a number of thoughts and recommendations about what should be included in post-approval studies that don't necessarily fit these four categories. So perhaps we could address these four categories and whether changes should exist for those and also the other elements.

Dr. Iglesia, do you want to begin?

DR. IGLESIA: Cheryl Iglesia.

Okay. So for pain, I actually thought that that TOMUS pain score that they used --

which it was good. Not only did you have, you know, the Likert scale, but I like the fact that patients could mark -- usually, if they have a picture, they can put an X over -- if you have pain, where it's located. That's very helpful, I think, and I would continue that and obviously with longer follow-up and looking at resolution. But I actually am -- I'm not as concerned about the pain, having seen the rate of resolution and then the smaller rate of de novo development of it. So also with prolapse, again, that's an extremely common scenario, and I think that that was probably present. And, you know, with time, more women are going to probably just get that just from aging and menopause.

DR. TALAMINI: So would you include it in a post-approval study?

DR. IGLESIA: Probably I would still include it. I'm more concerned about the development of significant prolapse after a sling -- after this fecal thing is in place. And then with regards to diagnostic surveillance, I think they actually have pretty good mechanisms of what they were -- the kinds of questions they were asking. The question about lost to follow-up is very important, and already you've had some lost to follow-up even here at the 3-year mark, and that's where these electronic patient-reported outcomes, in some format, whereas a patient could still be queried even though they may not be in the same location. If you have their electronic -- I mean, their e-mail address or something, where they can -- at least objectively. You know, because many people move, or if they have a complication, they're not going to be seeing the same surgeon who put that device in. So just some way of capturing that would be really important, and I know that some registries do that, including the PFDR. But that would be very important because that's where you'll capture, you know, the fact that I had to have another colostomy or I had a

perirectal abscess from an erosion that developed, you know, with this mesh, you know, by the rectum or something.

And then any other concerns. Well, my concern from the get-go in these post-approval -- while I do like the 5-year follow-up, I'm more concerned that we're not having any other comparison study, and I think that's just a lost opportunity, you know, for patients in terms of counseling and figuring out which patients this is -- identifying which patients are best for this specific procedure.

DR. TALAMINI: So what about imaging?

DR. IGLESIA: Well, when I say imaging, I'm interested in that for two reasons: preoperative imaging to determine the failures, and then postoperative diagnostic surveillance for what happens in vivo with this mesh and potential migration, et cetera.

DR. TALAMINI: So if you could design the ideal post-approval study --

DR. IGLESIA: Yes.

DR. TALAMINI: -- and include imaging --

DR. IGLESIA: Yes.

DR. TALAMINI: -- where would you put it, what imaging would it be, and at what intervals would it be?

DR. IGLESIA: Okay. Since I know for a fact that not everybody is as good as a pelvic floor diagnostician with ultrasound as Oklahoma, and not everybody has a John DeLancey, who's a super uber pelvic MRI, I think that in a subset of patients at some of these sites, it would be important to get that kind of information, which would help inform the others who are maybe not as expert, and then be able to help us in the future and figure out, you

know, maybe this woman who can't Kegel, she's got -- you know, that's the kind of person that maybe you would take to imaging and seeing oh, look, she doesn't have pelvic floor muscles. They're all detached from the pelvic side wall, and you know, this thing's not going to work for her. Go to Interstim or something. I have no idea. It would just be very interesting to look at if we could predict those failures.

DR. TALAMINI: So there's not one study that you would propose, that every patient gets pre and at some interval post? Your recommendation would be a subset of patients that has more sophisticated --

DR. IGLESIA: I like to be really -- I think I like to be practical about this. Yeah. I mean, not everybody can get a $2,000 pelvic MRI, and not everybody has the eyes to be able to find mesh. It does take some technique. So I think we can learn from the experts, and I don't think it would be too much of a burden to add that to a study, and there might be very valuable information for surgeons.

DR. TALAMINI: And any other concerns that should be included in a study that we haven't -- or that you haven't talked about or that we haven't talked about?

DR. IGLESIA: No, I was very happily -- I mean, I was happy to see that the rate of dyspareunia didn't seem to be there. I mean, obviously, this is a small study, but the PISQ seemed to not show that. And there is a pain question on the PISQ. And then, you know, on the PFDI, you know, there is an overall pain question, as well. I think they did a really good job in using the validated questionnaires, and they're the best that we have. I guess that the issue about defecations, straining, I'm not even sure of the best way to do that. Maybe defecography is probably the best modality in showing that, or even dynamic MRI,

but I'm not sure.

DR. TALAMINI: And I'm assuming that you are in favor of a post-approval study if this gets approved, yes?

DR. IGLESIA: Well, yeah. I'm --

DR. TALAMINI: Yes.

DR. IGLESIA: First of all, I'm in favor of approval, and I'm in favor of a post-approval study.

DR. TALAMINI: Dr. Inge.

DR. INGE: I don't have a whole lot to add to that. I guess I would just say, in response to Dr. Connor's comments about losing a comparison group, you know, I think that best practice research should be used, and they should be incentivized, and they should come back. They don't have any benefit to be gained, so they have to be incentivized.

DR. TALAMINI: Dr. Afifi.

DR. AFIFI: So, in aspiring to have an ideal study, I would have the following to suggest. In addition to these two groups, the continuation of the existing cohort and another one, in addition, recruit a comparison group that would not get the procedure but would be supplying data to be compared to the data obtained from the first two groups that we just talked about. So that's number one.

Number two, I would like to go back to the question of the ethnic/racial composition. I would urge the Sponsor to do serious effort in identifying clinics that have a large number of African-American patients and also clinics that have a large number of Hispanic patients. Very easy to find them by just looking at their existing data. We know

that certain states of certain regions have an abundance of these two ethnic groups. So that would give the Sponsor an opportunity to make up for the lack of them in the first part of the study. And similarly, in designing the sampling for the comparison group, that ethnic/racial composition should be also kept in mind to try to balance it to something that comes closer to what we know about in the U.S. After all, the white population is probably now only about 60%, going down to less than 50 in about 10-15 years. So we need to really be serious about that.

Thank you.

DR. TALAMINI: Thank you.

Dr. Hicks.

DR. HICKS: I don't have much to add, except to make sure that we pick either a digital or an anoscopy for the group, from the beginning forward, you know, to make sure there's no erosion issues. And I can't think. So maybe somebody will -- I have a brainstorm here some, but this whole issue about the pain, I don't know what you can garner from the get-go that would help us. I'm not sure if somebody could think of something that would be valuable data to garner before we start this study, but that seems to be the biggest problem that we've had. I'm not worried about the prolapse -- keep the data. But that's the one issue here, and I don't know. I hate to wait until the end of the study, then I wish we'd thought of that. It's one of those kind of moments. So if somebody has an idea, let me know otherwise.

DR. TALAMINI: Thank you, Dr. Hicks.

Dr. Efron.

DR. EFRON: Jon Efron.

I don't have anything else to add.

DR. TALAMINI: Do you have thoughts about specifically monitoring for erosion or --

DR. EFRON: Yes, I agree with Dr. Hicks. I think there should be a standardized follow-up, certainly within the first -- well, long term for 5 years on digital examination, at the very least, and whether anoscopy or other things are included. I think it's very, very important to qualify the pain prior to placement, and the same pain scale needs to be administered prior to the administration of the procedure and then for a period of time afterwards. As far as imaging or obstructive defecation, I think it's a very difficult problem. If you were to look purely at defecography done on normal individuals who don't have obstructive defecation, they have findings of obstructive defecation. So it's a very difficult thing to quantify, I would say. But those are my thoughts.

DR. TALAMINI: So a dummy question. Why not just a single-shot contrast study in the rectum? Would that be of no value? I mean, to monitor whether the angle has really been addressed, what's happening over time if there's a stricture?

DR. HICKS: Well, I mean, I think the first -- I think defecography on fecal incontinence patients is very difficult. So to really see the change in the angle and to actually do a defecogram on someone who's fecal incontinent is almost impossible. So I'm not so sure you can have pre- and post-findings. And, again, we're assuming that the anorectal angle is the issue for the improvement, but I don't know whether that's what's really causing the improvement or not.

DR. TALAMINI: That might be one way to find out, though.

DR. HICKS: Maybe.

DR. TALAMINI: Dr. Afifi.

DR. AFIFI: Just a quick postscript. I'm sorry, I didn't specifically mention the other ethnic/racial groups, the Asians and Native Americans and so on. By implication, I really meant all of the ethnic composition of the population.

DR. TALAMINI: Dr. Inge, you had an additional comment?

DR. INGE: I think Dr. Afifi has been making a plea based on general principles, and I think that that's fine. But in the experts here, is there a predilection or a predisposition of higher risk in your experience for these problems in African Americans or Hispanics or Asians, or is this more or less a problem of Caucasian women? Does it span all groups equally?

DR. TALAMINI: I think there was a mention earlier that the African-American population is relatively protected, but beyond that, I haven't heard other comments.

Dr. Kalota, do you want to comment on that, in addition to the post-approval study?

DR. KALOTA: Yes. I think that the African Americans have a lower incidence. I'm not certain about the other ethnic groups. I agree with everything that's been said before. Ideally, in my mind, we would have this study versus a control group with no intervention. Having done some research, if you don't give them any care, why would someone participate? So getting that control group would be nearly impossible, and if you got them, to keep them involved is definitely impossible. They're miserable. They want some treatment. So I don't think that it's going to be realistic to get a control group with no intervention. And the biggest issue for that would be the pelvic organ prolapse and the

incontinence, which I don't see as major issues. The pain, for me, knowing who had what pain before and who had what pain after would be important.

DR. TALAMINI: Okay. Dr. Hicks, an additional comment?

DR. HICKS: One thing would be if we keep good score for the patients who get pain, how they treated them. You know, really know, are they going to -- if you have a pen, are you going to inject them? How do they do -- so that you don't later lose that data. So going all on, if they have pain and they're treated for pain, they have to keep, you know, a log of how they tried to attack that problem.

DR. TALAMINI: The management of the pain as well as the pain itself.

DR. HICKS: Exactly. And the other thing would be -- I don't know if we have any epidemiologists here, but I would think there's got to be some studies about fecal incontinence in countries where you can't get it fixed, there are no surgical procedures, there's nothing. It would be interesting to see somebody who has to study where it goes because that way you don't -- that's where you get the control group and they can't have any possible treatment.

DR. TALAMINI: Ms. Berney.

MS. BERNEY: Well, I agree with the idea that you need to include a larger diverse group, but I also am aware that there are many studies that show that minorities (a) have less access to healthcare, and (b) are far more reluctant to discuss taboo subjects than white people. The studies have shown this. And I'm referring especially to in Rockford, where I live, where the Rockford Health Council has identified that this is a major problem, especially with things like blood pressure. They just don't go to the doctor. So it might be

difficult to get a subset that's going to be a cross-section in comparison to what the general populations of those minorities might be. That said, I think they need to diversify a lot better than they did. As far as the other issues, I think that what everybody else has said has been already -- it's already been said.

DR. TALAMINI: Okay, thank you.

Dr. Fennal.

DR. FENNAL: No additional comments.

DR. TALAMINI: Thank you.

Dr. Donatucci.

DR. DONATUCCI: Yeah, just a couple. And I preface my remarks by saying what I'm about to say is based upon men and not women. In my clinical time, in my clinical years, I did a lot of work with prosthetics in men, and in terms of erosion, it's not hard to find a true erosion. What you want to do is find an impending erosion and stop it before it actually erodes. There are a couple things that predispose. One is an irradiated pelvis, prior surgery. The combination of prior surgery and radiation is even worse, and then anything that might lead to compression or pressure over an implanted device. So rather than potentially studying everyone who gets the device and looking over time to see what happens, I think paying attention to people who are higher risk might be a better strategy. But again, that's men and I don't know -- although, frankly, erosion to the rectum should not really matter which gender that we're talking about.

DR. TALAMINI: Okay, thank you.

Dr. Connor.

DR. CONNOR: So, number one, I've said this many times, is the idea of just studying the benefits of stretching. I don't know that this is something I would recommend or require for FDA because, as you like to say, you do not regulate the practice of medicine. So I guess that's a recommendation for the Sponsor. It seems like a way to maybe increase the benefit of this procedure and device for patients. Two, I had written down that Dr. Hicks said this. It's just to understand, you know, what is required for patients who have pain. So perhaps, you know, track the percentage of patients who initiate, you know, opioid or narcotic use or however, you know, we measure hardcore pain that is due to pelvic pain, because obviously that could start through the hips or whatever, you know, a hip transplant or something like that.

So measure the number of patients with extreme pain who, you know, get tracked. That way we can understand that. I would ask patients just straight up, you know, at 6 months or a year or whenever, was your decrease in fecal incontinence worth any increase in pain you have? Because I can imagine, as a doc talking to a patient, saying 6% of women said the pain wasn't worth the benefit, you know, that means something versus 20%. So that would be an interesting number to know. You know, track the number of meshes that may have to be tried to explant. I mean, that's something that seems like, long term, is worth thinking about. And then something we haven't discussed, but it came up on one of the slides that we saw after lunch, is that patients with no external sphincter defect -- and I have no idea what that means -- did worse. So that's just maybe something worth measuring down the line to understand if those patients are different and should be treated differently.

DR. TALAMINI: Thank you.

In looking at (c) carefully, I'm not sure we've hit the mark on that question, if I'm understanding the verbiage. It says, "Does the Panel have recommendations about the method or scheduled diagnostic surveillance for following subjects in relation to other adverse events?"

Dr. Fisher, do you mean -- are you looking for the Panel's opinion of what study should be undertaken in the event of a patient having an adverse event in this post-approval study? Because, if so, I don't think we've answered that question.

DR. FISHER: No, I think we identified some serious adverse events when we were going through, including some other ones, like infections. I think it was just meant as a general question. Is there anything else that we should take into consideration?

DR. TALAMINI: Okay. Dr. Faulx, do you -- if you're still on the line, do you have thoughts about this post-approval study, as we've been discussing?

DR. FAULX: I don't really have anything further, no.

DR. TALAMINI: Okay, thank you.

Sir. No, behind you.

DR. BAYONA: Just one more element here that hasn't been discussed: the schedule. We were concerned about the discussion that was already done here in this Panel about evaluation of the patients during the first year. As it is now, the Sponsor is planning to examine the patients -- and then every year. And we believe that perhaps examining the patients at 3, 6, and 9 months during the first year is when most of the adverse events happening would be really the --

DR. TALAMINI: So let's proffer that question. How often should the patients be monitored for the first year? How often should they be monitored beyond the first year?

Dr. Connor.

DR. CONNOR: So I was going to ask first, does that increase the burden or cost to patients if they're having to come back to say everything's okay, doc?

DR. TALAMINI: I don't think we're supposed to consider the cost considerations directly.

DR. CONNOR: Yeah. And I was just trying to figure out, in terms of being patient centered, not to, you know --

DR. TALAMINI: Got it.

DR. CONNOR: And I'll remove the cost part, but --

DR. TALAMINI: Well, most patients -- this is Talamini. Most patients, following any significant procedure, are going to be seeing their surgeon on some sort of a regular basis for some period of time.

DR. CONNOR: Right, right.

DR. TALAMINI: So it's an expected behavior.

DR. CONNOR: Okay. So I think that's the answer. If they're coming back anyway, then asking these particular questions to make sure we don't miss something, it seems valuable.

DR. TALAMINI: Dr. Iglesia, for this study, what intervals?

DR. IGLESIA: I do think that adding a 6- and 9-month would be very burdensome for patients and providers. Generally speaking, I mean, when we see patients even for

implants, it's 2 weeks, and then somewhere between 8 to 12. So you'll see them in 2 weeks, and then you'll see them at the 1-year follow-up. So to add a 6 or a 9, that would be a study visit, which, you know, I probably wouldn't want to be paying, I mean charging for their insurance with their added co-pay. But if that's an important variable in a subset of patients, then perhaps we can do that. And I know that in some of the 522 studies that we've done for the FDA, it was, you know, every 6 months for 3 years. But in general, 3 months and 12 months is what I would -- and then bye-bye, you know.

DR. TALAMINI: So you'd vote 3 months and 12 months?

DR. IGLESIA: Um-hum.

DR. TALAMINI: Okay.

Dr. Inge.

DR. INGE: I agree with that.

DR. TALAMINI: Dr. Afifi.

DR. AFIFI: I would like to leave that to the clinicians.

DR. TALAMINI: Dr. Hicks.

DR. HICKS: On the question, I would agree -- I would question, in the original study, were the patients charged? As you followed them up, did they get a regular charge to their insurance company, or did you all pick it up?

MR. BELOW: I'm Paul Below.

We paid for all the procedures in the pivotal study.

DR. TALAMINI: But really we want to design the best study and not worry so much --

DR. INGE: Well, the best study would be they pay for it.

(Laughter.)

DR. TALAMINI: Well, okay. So let's assume they pay for it. How often would --

DR. INGE: Well, okay. I would say you want to see them postoperatively within probably a week or two, depending if you're worried about the wound. And then I'd want to follow them out and see how they're doing maybe at 3 months, 6, 9, and then maybe at a year and then change. And if everything's going great there, then I'd tell them, you know, a yearly exam or come back if you have a problem. But I think that's what the problem -- that you would think an issue would happen in that first 12-month period, you'd think, if something significant is going to happen.

DR. TALAMINI: Dr. Efron, what would your schedule be for this study?

DR. EFRON: I think I would say initial postoperative follow-up followed by 3 and 12 months, and then yearly after that for a period of 60 months, which is what we're talking about.

DR. TALAMINI: Dr. Kalota, what would your schedule be?

DR. KALOTA: My schedule would be the same as I normally do, which would be a week, a month later, 3 months, and then yearly.

DR. TALAMINI: Okay. Ms. Berman. Berney, sorry.

MS. BERNEY: Well, as a patient who's now facing my 16th surgery, I would say that generally I am seen a week to 2 weeks after surgery, and usually 6 weeks, 3 months, and then bye-bye until next year unless you have a problem. So I would agree with that schedule.

DR. TALAMINI: Okay. Dr. Fennal.

DR. FENNAL: I agree with what has been said.

DR. TALAMINI: Dr. Donatucci.

DR. DONATUCCI: I have nothing to add.

DR. TALAMINI: Okay. Well, that was complex, Dr. Fisher, but the Panel certainly agrees on the importance of a post-approval study in the event of the device being approved. Lots of discussion, and it sounds like most Panel members agree that the frequency should be more than 3 months and a year. There's a strong sense that the diversity should be increased in a post-approval study; that there may be better ways to look at the pain, including how the pain is managed and not just the fact of whether the pain is there or not; tracking any explants or procedures that need to be undertaken to address the mesh itself in any way, cutting it, stripping it, attempting to remove it; and some mechanism of monitoring for potential erosion. There was disparity about imaging, but I think the strongest suggestion was that there be a subgroup that is intentionally studied, in terms of imaging, to try and determine the mechanism that's really driving this improvement. And there was also a subgroup of Panel members that felt strongly that there should be a comparative group, if possible, to improve a post-approval study.

Panel, did I miss anything? No.

Dr. Fisher.

DR. FISHER: The one point that I did hear is that this could be an area that's ripe for a patient preference survey, to either take the ongoing group that's still on or the new group and say is the pain worth the gain.

DR. TALAMINI: Yeah. All right, I think our remaining task is to actually vote, and what I would propose is that we take a 5-minute break before we begin that process. So we'll adjourn just for 5 minutes, and then we'll pick back up.

Thank you.

(Off the record at 4:42 p.m.)

(On the record at 4:50 p.m.)

DR. TALAMINI: Okay, let me call us back to order. Folks, we'll reconvene. The time is now 4:50. At this time the Panel will hear summations, comments, or clarifications from the FDA. The FDA has 5 minutes if they have summations, comments, or clarifications.

DR. FISHER: Not really a lot of summation. I would just like to thank everybody that came today, especially the patients. I think it's very valuable to hear the voice of the patients, and I think it was beneficial to everybody here. Once again, I said I think it was -- that this is an area ripe to still gather some information as to what is the tradeoff, how much pain would a patient accept for the gain that this is willing to offer them? I think that that's a valuable piece of information. We got a lot of information and suggestions and comments on the post-approval study. So I think that if we go into that direction, we have a lot of information that we can work with the Sponsor on in designing that study. So with that, I'd like to thank the Sponsor. I'd like to thank the patients that came today, and of course, the Panel.

DR. TALAMINI: Thank you, Dr. Fisher.

At this time the Panel will hear summations, comments, or clarifications from the Sponsor. Five minutes, please.

DR. FENNER: Well, I don't think we're going to take that amount of time. It's been a long day, certainly for ASTORA and for those of us, the clinical investigators and more importantly for the patients, that participated in this trial and hopefully those who will benefit from this product. We'd like to thank you for your time and attention for reviewing a large Panel pack and for being so attentive to the detail of the study. As you heard today, this is a patient population looking for an alternative to treatment for a very debilitating disease. As we saw from TOPAS, we have highly efficacious results with a device that has a positive safety profile. Over the 509 years of patient follow-up, the efficacy was durable. Again, we just want to thank you for review of the data. As we heard from the patients, they are willing to accept the potential risk for a treatment that will allow them to engage in their lives.

Thank you.

DR. TALAMINI: Thank you very much.

Before we proceed to the Panel vote, I would like to ask our non-voting members, Dr. Fennal, our Consumer Representative; Dr. Donatucci, our Industry Representative; and Ms. Berney, our Patient Representative, if they have any additional comments.

Dr. Fennal, if you could start, please.

DR. FENNAL: Thank you so much for the opportunity to serve on this Committee.

DR. TALAMINI: Thank you, Dr. Fennal.

Dr. Donatucci.

DR. DONATUCCI: I have nothing further.

DR. TALAMINI: Thank you.

And, Ms. Berney, any comments?

MS. BERNEY: Yes, I'd like to thank you for inviting me to participate in this Panel. As a patient, it is very important to me be the voice of patients. So thank you very much.

DR. TALAMINI: Thank you. And we appreciate your input greatly.

Okay, we are now ready to vote on the Panel's recommendations to the FDA for the TOPAS Treatment for Fecal Incontinence Device. The Panel is expected to respond to three questions related to safety, effectiveness, and benefit versus risk. Lieutenant Commander Garcia will now read three definitions to assist in the voting process. Lieutenant Commander Garcia will also read the proposed indication for the statement -- for use statement for this device.

Lieutenant Commander Garcia.

LCDR GARCIA: Thank you, Dr. Talamini.

The Medical Device Amendments to the Federal Food, Drug and Cosmetic Act, as amended by the Safe Medical Devices Act of 1990, allow the Food and Drug Administration to obtain a recommendation from an expert Advisory Panel on designated medical device premarket approval applications that are filed with the Agency. The PMA must stand on its own merits, and your recommendations must be supported by safety and effectiveness data in the application or by applicable publicly available information.

The definitions of safety, effectiveness, and valid scientific evidence are as follows:

Safety, as defined in 21 C.F.R. 860.7 - There is reasonable assurance that a device is safe when it can be determined, based upon valid scientific evidence, that the probable benefits to health from use of the device for its intended uses and conditions of use, when

accompanied by adequate directions and warnings against unsafe use, outweigh any probable risks.

Effectiveness, as defined in 21 C.F.R. 860.7 - There is reasonable assurance that a device is effective when it can be determined, based on valid scientific evidence, that in a significant portion of the target population, the use of the device, its intended uses and conditions of use, when accompanied by adequate directions for use and warnings against unsafe use, will provide clinically significant results.

Valid Scientific Evidence, as defined in 21 C.F.R. 860.7, is evidence from well-controlled investigations, partially controlled studies, studies and objective trials without matched controls, well-documented case histories conducted by qualified experts, and reports of significant human experience with a marketed device from which it can fairly and responsibly be concluded by qualified experts that there is reasonable assurance of the safety and effectiveness of a device under its conditions of use. Isolated case reports, random experience, reports lacking sufficient details to permit scientific evaluation, and unsubstantiated opinions are not regarded as valid scientific evidence to show safety or effectiveness.

The valid scientific evidence used to determine the effectiveness of a device shall consist principally of well-controlled investigations, as defined in paragraph (f) of this section, unless the Commissioner authorizes reliance upon other valid scientific evidence which the Commissioner has determined is sufficient evidence from which to determine the effectiveness of a device, even in the absence of a well-controlled investigation.

The Sponsor has proposed the following indication for use:

The TOPAS Treatment for Fecal Incontinence is intended to treat women with fecal incontinence, also referred to as accidental bowel leakage, who have failed more conservative therapies.

Panel members, please use the buttons on your microphones to place your vote of yes, no, or abstain to the following three questions.

Voting Question No. 1: Is there reasonable assurance that the TOPAS Treatment for Fecal Incontinence device is safe for patients who meet the criteria specified in the proposed indication?

Please vote yes, no, or abstain.

(Panel vote.)

LCDR GARCIA: Voting Question No. 2 reads as follows: Is there a reasonable assurance that the TOPAS Treatment for Fecal Incontinence is safe -- is effective -- let me start over, please. Is there a reasonable assurance that the TOPAS Treatment for Fecal Incontinence is effective for use in patients who meet the criteria specified in the proposed indication?

Please vote yes, no, or abstain.

(Panel vote.)

LCDR GARCIA: The third and final voting question reads as follows: Do the benefits of TOPAS Treatment for Fecal Incontinence outweigh the risks for use in patients who meet the criteria specified in the proposed indication?

Please vote now, yes, no, or abstain.

(Panel vote.)

LCDR GARCIA: Okay, I'm just going to take a moment here and tally up the votes.

(Tally of votes.)

LCDR GARCIA: Ladies and gentlemen, the votes have been captured, and I will read the votes into the record.

On Question 1, the Panel voted yes 8, abstain 0, no 0 that the data shows reasonable assurance that the TOPAS Treatment for Fecal Incontinence device for the treatment of fecal incontinence is safe for use in patients who meet the criteria specified in the proposed indication.

On Question No. 2, the Panel voted 8 yes, 0 abstain, 0 no that there's reasonable assurance that the TOPAS Treatment for Fecal Incontinence for the treatment of fecal incontinence is effective for use in patients who meet the criteria specified in the proposed indication.

On Question 3, the Panel voted 8 yes, 0 abstain, and 0 no that the benefit of the TOPAS Treatment for Fecal Incontinence device for the treatment of fecal incontinence outweigh the risk for use in the patients who meet the criteria specified in the proposed indication.

The three voting questions are now complete, unanimously.

DR. TALAMINI: Thank you, Lieutenant Commander Garcia.

I will now ask the Panel members to discuss their votes. If you answered no to any question, which is not the case, please state whether changes to labeling, restrictions on use, or other controls would make a difference in your answer. Please state your name and how you voted for each question for the record.

Dr. Kalota, could we begin with you?

DR. KALOTA: Susan Kalota.

I voted yes for all.

DR. TALAMINI: Do you want to add any comments?

DR. KALOTA: I think we had plenty of that.

DR. TALAMINI: Okay, thanks.

(Laughter.)

DR. TALAMINI: Dr. Efron.

DR. EFRON: Jon Efron.

I voted yes for Questions 1, 2, and 3. No comments.

DR. TALAMINI: Thank you.

Dr. Hicks.

DR. HICKS: Terry Hicks.

I voted for all three. I voted yes.

DR. TALAMINI: Thank you.

I did not have to vote as the tie breaker.

Dr. Afifi.

DR. AFIFI: I voted yes on all three questions. I have no further comments.

DR. TALAMINI: Thank you.

Dr. Inge.

DR. INGE: Tom Inge, Cincinnati.

I voted yes on all three questions, and I have no further comments.

DR. TALAMINI: Thank you.

Dr. Iglesia.

DR. IGLESIA: Cheryl Iglesia.

Yes to all. And I said enough.

DR. CONNOR: Jason Connor.

Yes to all and nothing more to add.

DR. TALAMINI: Okay, I would like to thank the Panel. Personally, you guys have really worked hard today, and you focused. Some of the questions were not easy. You've wrestled them all the way to the ground. Very, very grateful. It's been, I think, informative. It's been in many ways fun, and I think we really worked the questions hard. So I want to thank each and every one of you for your hard work today. I want to thank, in particular, our Patient Representative, Industry Representative, and Dr. Fennal as well for your input and your thoughts.

Dr. Fisher, any final remarks?

DR. FISHER: For anyone who came from out of town, we threw thunderstorms at you, we threw hail at you, we threw tornados around the area, but it didn't stop you from coming. And snow. That's right, snow of you guys up north. So I really want to thank everyone who traveled in last night, despite the weather and the delays and everything. I really appreciate it, and we couldn't do it without you. And a safe journey home.

DR. TALAMINI: Thank you.

So with that, we'll pronounce the October -- today's not October --

(Laughter.)

DR. TALAMINI: -- the February 25th, 2016 meeting of the Panel adjourned. Thank you.

(Whereupon, at 5:05 p.m., the meeting was adjourned.)

C E R T I F I C A T E

This is to certify that the attached proceedings in the matter of:

GASTROENTEROLOGY AND UROLOGY DEVICES PANEL

February 25, 2016

Gaithersburg, Maryland

were held as herein appears, and that this is the original transcription thereof for the files of the Food and Drug Administration, Center for Devices and Radiological Health, Medical Devices Advisory Committee.

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CATHY BELKA

Official Reporter